New Orleans Medical
and
Surgical Journal

$4.00 Per Annum, 35c Per Copy
Vol. 103, No. 11

MAY, 1951

Published Monthly
1430 Tulane Avenue, New Orleans 12, La.

A CLINICAL REVIEW OF THE NEURALGIAS OF THE HEAD*

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Although the term "neuralgia" has been used by physicians for centuries it is well to define it before proceeding with this discussion and to distinguish it from neuritis. Neuralgia is a sharp intermittent pain in the distribution of a given nerve without apparent cause. The idiopathic nature of the disease is not an essential part of the definition at present. Often careful neurologic or anatomic study in a case of sharp intermittent pain in the distribution of a nerve may suggest some organic lesion, inflammation or a metabolic, vascular, toxic or structural defect. Aneurysms, localized infections and tumors have been described repeatedly as etiologic factors in one or the other forms of major tic douloureux. Then too an introspective psychiatric evaluation often gives ample reasons for the "painful syndrome of unknown origin." The treatment is obviously more successful when the cause is discovered.

The pain of neuritis unlike the pain called "neuralgia" is continuous and is usually accompanied by tenderness, paresthesia, anesthesia, and possible motor paralysis if a mixed nerve is afflicted. Irritation or inflammation of the peripheral neurons is the cause of neuritis and a lesion of the central neurons is presumed to be responsible for neuralgia if no other etiologic factor is found. The two nerves most frequently involved in neuralgia from a clinical standpoint are the fifth and ninth cranial nerves; hence trigeminal neuralgia and glossopharyngeal neuralgia can be regarded as major forms of neuralgia (table 1).

TABLE 1

THE MAJOR AND MINOR TYPES OF NEURALGIAS AND OTHER PAINFUL CONDITIONS OF THE HEAD

I.	**Major types of neuralgia**
	A. Trigeminal neuralgia
	B. Glossopharyngeal neuralgia
II.	**Minor types of neuralgias**
	A. Occipital neuralgia
	B. Postherpetic ophthalmic neuralgia
	C. Superior laryngeal neuralgia
	D. Sphenopalatine neuralgia (syndrome of Sluder)
	E. Tympanic neuralgia (syndrome of Reichert)
	F. Vidian neuralgia (syndrome of Vail)
	G. Geniculate neuralgia (syndrome of Ramsay Hunt)
III.	**Other painful conditions**
	A. Migraine
	B. Histaminic cephalalgia
	C. Costen's syndrome
	D. Psychogenic pain
	E. Temporal arteritis
	F. Miscellaneous conditions

MAJOR TYPES OF NEURALGIA

Trigeminal Neuralgia. Trigeminal neuralgia usually affects patients beyond the fourth decade of life. It is rarely bilateral and usually involves one or more branches of the fifth cranial nerve on one side of the face. Excruciating, paroxysmal and flash-like jabs of pain are characteristic of the syndrome. Krause[1] has credited Avicenna

*Presented at the meeting of the New Orleans Graduate Medical Assembly, New Orleans, Louisiana, March 8, 1951.

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with describing the symptoms as *"tortua facies"* about 1,000 A. D., and Fothergill with describing the disease as a "painful affection of the face" in 1773. Many others contributed subsequently to the treatment, but as in many other diseases, little has been added to the original description of symptoms. Injections of absolute alcohol into the involved branches of the fifth cranial nerve will give palliative relief, and permanent relief can be obtained from section of the sensory root of the gasserian ganglion. The temporal approach, as developed by Frazier and Spiller[2], has been the procedure of choice throughout the world for interrupting the pathways of pain through the sensory root of the fifth nerve. In recent years, however, Dandy's procedure[3] and that of Sjöqvist[4] have been used. In Dandy's procedure the nerve is cut close to the pons and in Sjöqvist's the descending root of the fifth nerve is cut in the medulla.

Glossopharyngeal Neuralgia. Glossopharyngeal neuralgia occurs less frequently than trigeminal neuralgia. The intermittent and paroxysmal pain is like that of trigeminal neuralgia but it occurs only in the area innervated by the ninth cranial nerve. The branches of this nerve supply sensory fibers to the ear, the pharynx, the tonsils, and the tongue. Neuralgia in areas of distribution of this nerve may involve any one of the branches or all of the branches as in trigeminal neuralgia. The trigger zone is mainly in the throat about the tonsillar fossa. Except for the location of the pain, cocainization of the tonsillar region on the affected side is the best method of differentiating between the two major forms of neuralgia. The diagnosis of glossopharyngeal neuralgia can be confirmed if the swallowing of cold water always precipitates a paroxysm of pain and if cocainization of the pharynx and tonsillar region with 10 per cent cocaine abolishes this pain reflex. Intracranial section of the ninth cranial nerve will give permanent relief of glossopharyngeal neuralgia. The postoperative anesthesia extends over half the pharynx, glottis, epiglottis, uvula, and tonsillar area. Of this, however, the patient rarely complains.

MINOR TYPES OF NEURALGIA

Occipital Neuralgia. Although occipital neuralgia is usually unilateral it may be bilateral. When it is bilateral one side is likely to be more severely affected than the other. Pain invariably begins in the back of the neck below the mastoid process, extends over the side of the head and often centers behind the eye on the side affected. Pain back of the eye is due to close anatomic association of the descending root of the ophthalmic division of the fifth cranial nerve in the cervical cord and the origin of the greater and lesser occipital nerves. Block of the second cervical nerve with procaine hydrochloride will help in establishing the diagnosis of occipital neuralgia. To control the pain it may be necessary to use cervical traction, repeated injections of the nerve or rhizotomy of the sensory roots of the second and third cervical nerves.

Postherpetic Ophthalmic Neuralgia. Herpes zoster of the ophthalmic division of the trigeminal nerve affects mainly the supraorbital and supratrochlear branches. The neuralgic pain is excruciating and disabling and satisfactory treatment is very difficult. A virus infection is thought causative and hence such antibiotics as aureomycin and streptomycin may give some hope of relief if used in the early stages of the disease. Roentgen therapy directed over the geniculate ganglion also is helpful in the early stages of the disease. Injections of alcohol and avulsions of the involved nerves may offer temporary relief. Relief has not been obtained from sectioning of the posterior sensory root of the fifth cranial nerve in many cases, and prefrontal lobotomy has been necessary to interrupt the appreciation of pain from a mental standpoint in some such cases.

Superior Laryngeal Neuralgia. The pharyngeal plexus receives fibers from the glossopharyngeal nerve, the sympathetic nerves and the superior laryngeal nerve. It is unknown whether superior laryngeal neuralgia which is localized in the side of the neck opposite the thyroid cartilage is a dis-

tinct clinical entity or whether it is an atypical or incomplete form of glossopharyngeal neuralgia brought about through anastomosis with the ninth cranial nerve in the pharyngeal plexus. Swallowing or touching the trigger zone with an instrument produces paroxysms of lancinating pain. It seems to extend from the side of the thyroid cartilage or from the trigger area in the pyriform sinus to the angle of the jaw and occasionally to the ear. If procaine hydrochloride block of the internal branch of the superior laryngeal nerve will relieve the characteristic paroxysms of pain the nerve can be approached through an incision in the neck and interrupted distal to the ganglion nodosum. If more extensive measures are indicated intracranial section of the ninth cranial nerve together with interruption of the uppermost rootlet of the tenth nerve will give permanent relief.

Sphenopalatine Neuralgia (*Syndrome of Sluder*). Sluder[5] described various patterns of pain of the head and neck which he considered due to sphenopalatine neuralgia. At present, however, these seem to be due to a vasodilating type of headache and may be reflexly controlled by the sympathetic nerves. Sphenopalatine neuralgia is often described as headache of the lower half of the head. The pain has a wide distribution; it may be in the root of the nose, in the orbital area, in the upper jaw and teeth, in the temple, zygoma, the ear, the mastoid, the occiput, and the neck. It may extend to the shoulder and arm and even fingers. The same group of symptoms has been presented by patients when the etiologic factor has been in the cervical portion of the spinal column. In such cases the pain in the occiput and head has been considered as a reflex phenomenon due to stimulation of the sympathetic nerves and the descending roots of the trigeminal nerve in the spinal cord, or even to pain distributed over the vascular tree to the vertebral artery or to the branches of the external carotid artery. The removal of the lesion in the cervical area has controlled the pain. The reverse may occur also with a focus in the sinuses, or allergic manifestations may be the trigger for such troubles. A histamine-like reaction or vasodilation is invariably the rule.

Injections into the sphenopalatine ganglion or cocainization of the posterior tip of the middle turbinate just over the ganglion with 20 per cent solution of cocaine has given relief in many cases. Sluder[6] also suggested that cure or help for the pain would be obtained by the application of 2 per cent solution of silver nitrate, or 0.5 per cent solution of formaldehyde to the same part of the nose. Horton[7] recommended a program of desensitization when a typical attack is provoked by histamine.

Tympanic Neuralgia (*Syndrome of Reichert*). Reichert,[8] in 1933, called attention to the fact that an incomplete form of glossopharyngeal neuralgia should be recognized. The neuralgic pain which is distributed through the tympanic branch of the glossopharyngeal nerve (or Jacobson's nerve) represents an incomplete neuralgia of the glossopharyngeal nerve. Reichert proved that intracranial section of the ninth cranial nerve permanently cured the otalgia.

Vidian Neuralgia (*Syndrome of Vail*). Vail[9] defined vidian neuralgia as a pain of neuralgic character in the nose, face, eye, ear, head, neck, and shoulder occurring in severe attacks. In his opinion the attacks are most typically unilateral, are often nocturnal, may or may not be associated with the subjective symptoms of nasal sinusitis and cannot be caused by any external stimulation. The pain is not relieved by opiates and is not associated with any subjective loss of sensation.

The distribution of the painful symptoms in vidian neuralgia was explained by Vail as follows: The great superficial petrosal nerve comes from the geniculate ganglion of the facial nerve; the great deep petrosal nerve is formed by the branch from the carotid plexus and the small deep petrosal nerve from the petrous ganglion of the glossopharyngeal nerve. Thus, through the nerves uniting to form the vidian nerve, there is a close tie-up between the sphenopalatine ganglion, the geniculate ganglion of the facial nerve, the superior cervical

sympathetic ganglion, the glossopharyngeal nerve and the vagus nerve. The orbital, nasal, and palatine branches pass from the sphenopalatine ganglion and it is easy to explain the referred pain in the eye, nose, and teeth. The pain in the ear, a typical and characteristic part of the syndrome of vidian neuralgia, has a little more complicated explanation.

Geniculate Neuralgia (Syndrome of Ramsay Hunt). It is rare indeed to encounter a case in which severe pain in the ear and deep structures of the face is the result of disease of the geniculate ganglion, or sensory ganglion of the seventh cranial nerve. The patient who has undergone resection of the posterior sensory root of the gasserian ganglion for trigeminal neuralgia often will complain of a bizarre feeling in the deep structures of the face which may be attributed to the sensory preservation of the seventh nerve and chiefly to contraction of the facial muscles. This is regarded as an annoying pain but not as neuralgia. Several cases have been reported in the literature, however, which provide authoritative proof that the seventh nerve can be responsible for a severe ticlike intermittent pain. In every case reported permanent relief has been obtained by intracranial section of the nerve of Wrisberg.

Hunt investigated the herpetic, inflammatory lesions of the geniculate ganglion. He published his first report in 1907[10] and continued that study for many years thereafter. He has made outstanding contributions to our knowledge of the sensory system of the facial nerve and its neuralgic conditions. He asserted that geniculate neuralgia is a real clinical entity and that it belongs in the field of atypical facial neuralgias. It is possible that he is correct. In this connection, it is also important to recall that a large group of neurologists and neurosurgeons, as well as otolaryngologists, have been screening their cases for forty years and only three authentic reports of relief of pain by intracranial section of the nerve of Wrisberg have appeared in the literature. One must assume, therefore, that this form of neuralgia is rare and that other forms of treatment, such as section of the glossopharyngeal nerve, may control the pain in many cases.

OTHER PAINFUL CONDITIONS OF THE HEAD

From a differential standpoint, other painful conditions of the head must be separated from the true neuralgias. The commonest conditions are histaminic cephalalgia, Costen's syndrome,[11] temporal arteritis, "jumping toothache," migraine, arteriosclerotic headache, pain of hemifacial atrophy, and psychogenic pain.

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BLOOD CHANGES WHICH PREDISPOSE TO SHOCK IN THE POSTOPERATIVE AND POSTDELIVERY PHASE

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Many factors predispose to shock in postoperative or postdelivery patients. The important contributory causes include blood loss, debilitating diseases, endocrine upsets, states of exhaustion or dehydration, excessive trauma, and improper sedation or anesthesia. Of these conditions mentioned, hemorrhage is the one most frequently found in association with shock.

The complete subject of shock has many aspects. I have chosen one particular phase. This is referable to those changes in the blood and circulation which predispose to hemorrhage and shock. Though most of our investigative work has been on obstetrical patients, the general principles involved are applicable to the patient subjected to any operative procedure.

ANEMIA

Anemia in pregnancy or in the preoperative patient is not an uncommon finding. No matter what type may be diagnosed, the untreated case has a predisposition to hemorrhage and shock at the time of operation or delivery. Routine investigation should be advised for every patient and suitable

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Presented at the Fourteenth Annual Meeting of The New Orleans Graduate Medical Assembly, March 5, 1951.

treatment is indicated when anemia is found.

Our first chart is self explanatory. These were 500 clinic cases taken in a consecutive manner. They were all examined before the twelfth week of pregnancy.

TABLE 1
ANEMIA

Hemoglobin	Percentage	500 cases
90 and higher	16)	No evident
80 to 89	28)	anemia
70 to 79	31	Slight anemia
60 to 96	20	Moderate anemia
59 and lower	5	Marked anemia

The majority of patients who suffer from anemia are included in the iron deficiency group. These usually respond to proper diet supplemented by some form of iron therapy. If there is not a response to this type of therapy the patient should have a thorough investigation of the blood.

Special examinations, the hemogram, and bone marrow studies are not always available to the general doctor. However, with reference to the patient who does not respond to ordinary treatment special procedures are imperative. Some of our most serious cases have been proven to have rare types of anemia such as the macrocytic or megaloblastic varieties; in addition, Beacham and Beacham[1] in a recent paper have emphasized the relationship of sickle cell anemia to high incidence of shock.

BLOOD LOSS

Authors such as Eastman, Peckham, and Conn[2-4] emphasize the importance of certain conditions which influence blood loss. It is observed that operative delivery causes three times as much bleeding as spontaneous delivery; this is possibly due to lacerations and the increased amount of anesthetic agents employed. The management of the third stage of labor and its duration cause marked variation in blood loss. As recently as 1949, Gilliatt[5] stated hemorrhage was still the greatest direct or indirect cause of maternal death, as well as contributing largely to sepsis and thromboembolic disease. Scott[6] observed in his survey that the great majority of cases with obstetrical shock could be evaluated in terms of hemorrhage. (Figure 1).

FIG. 1

BLOOD LOSS MEASURED IN NORMAL CHILDBIRTH (1919-1948)

NAME	NO. OF CASES	AVERAGE BLOOD LOSS c.c.	NAME	NO. OF CASES	AVERAGE BLOOD LOSS c.c.	
WILLIAMS	1000	343	PASTORE	500	242	
LITZENBERG	3002	462	CONN	800 PRIMP	388	323
				1200 MULTIP	280	
DE LEE		500				
AHLFELD		500	BICKERSTAFF	2015	150	
TARNIER		600	DAVIS	1000	150	
PLASS	1157	317	QUIGLEY	430	211	
CALKINS		179	WHITE	300	273	
BRANDT		195	CARROLL	70	301	
		RANGE 150 - 600 m.				

Blood loss at the time of operation or delivery is usually inaccurately estimated by the surgeon and his assistants. This is unfortunately true in the field of obstetrics where we have been rightly criticized for our underestimation of blood loss and for the lack of adequate treatment in such cases.

The estimation of hemorrhage is difficult and inaccurate by visual observation or by most methods of direct measurement. It has also been suggested that all blood loss is not apparent and that it does not totally escape through the vaginal tract. Probably some is retained in the uterine sinuses, in the birth canal or in bruised surrounding tissues.

In addition, many women have been observed in the early puerperium who are tired, pale and exhausted. This was to an extent comparable to cases of severe medical and surgical emergency such as bleeding peptic ulcers where the known hemorrhage was between 2 and 3 litres. But estimated blood loss was small in these obstetrical individuals; the hemoglobin concentration and red blood cell counts did not manifest as low a level as would be expected from clinical observation. This in itself has restrained many attending obstetricians from resorting to early blood transfusion. There appeared to be something wrong with the methods of estimating blood loss and the correction of the condition. For these

reasons a few investigators turned their interests toward blood volume studies.

BLOOD VOLUME STUDIES

Since 1938 there have been several series of articles in addition to our published results referable to blood volume changes during pregnancy and in the postpartum period. The principle changes which occurred during pregnancy and postpartum are shown in figures 2 and 3.

FIG. 2

BLOOD LOSS IN NORMAL CHILDBIRTH CALCULATED FROM BLOOD VOLUME CHANGES

			AVERAGE LOSS		
NAME	DATE	NO. OF CASES	RED CELLS ml.	WHOLE BLOOD ml.	METHOD
THOMSON ET AL.	1938	15	329	1163	T-1824 DYE
McLENNAN AND THOMIN	1948	20	283	810	T-1824 DYE
CATON ET AL.	1949	10	318	947	T-1824 DYE
TYSOE AND LOWENSTEIN	1949	13	430	1248	T-1824 DYE
RATH, CATON ET AL.	1950	21	500	1250	RADIOACTIVE ERYTHROCYTES
	RANGE		810 - 1250 ml.		

FIG. 3

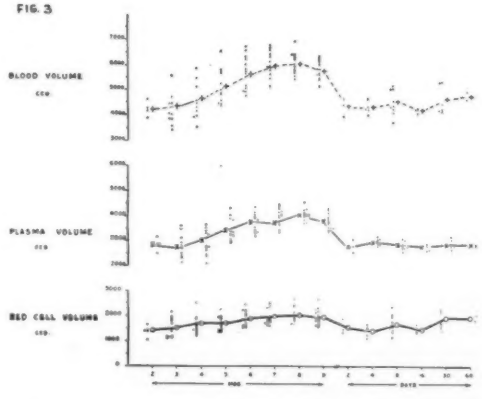

Figure 3: Blood volume changes which occur in normal pregnancy and in the post-partum period. Tysoe & Lowenstein.

All investigators used T1824 dye except Dieckman[7] who employed a vital red of which the composition is uncertain. Subsequently, Caton and his co-workers published a series in which they employed T-1824 dye to determine plasma volume and they used radioactive erythrocytes to simultaneously determine the red cell mass. But none of these investigators attempted to determine blood loss by comparing red cell volume immediately before and shortly after delivery.[8-11]

Relative studies have been accomplished in other fields of medicine; these have a direct bearing on the subject. As early as 1938, Bennett[12] studied blood volume changes in cases of severe blood loss from gastroduodenal hemorrhage. He was able to control immediate preoperative and postoperative treatment by determining the red cell mass. Because of the deceptive nature of hemoglobin and hematocrit estimates he felt that his methods were not only relatively accurate but that they were life saving. Coller[13] and his associates studied blood losses in surgical operations. They believed that the losses were considerably higher than had formerly been thought. Clark[14] and Ochsner described a condition of reduced blood volume in the chronically ill patient which they have labelled, "chronic shock." And Lyon[15] has followed surgical blood loss by dye methods, finding that the blood loss as determined by blood volume was greater than that found by other means.

During the last four years Wilson[16] has been following changes in the blood volume immediately preoperative and postoperative. He has tried to wait until the bleeding has been controlled, but he believes that his results are of value even when they are subject to such causes of error as blood transfusion continuing during his estimation. He found excellent correspondence in many cases between blood loss and blood volume fall within the experimental errors of the methods. He feels that when a discrepancy exists between blood loss and blood volume fall, it may mean that, during severe operations, a fraction of the blood volume stagnates and passes out of effective circulation. Anoxia and the danger of life would then be out of proportion to the quantity of blood lost.

After considering the above, it seemed feasible and justifiable to attempt to determine whole blood loss from the circulation at the time of childbirth. The plasma volume at the time of delivery changes rapidly and unpredictably due to exertion and hormonal influences. This alters the total

blood volume and renders it impossible to determine actual blood loss by subtracting the postpartum from the antepartum total blood volume. However, the red cell volume is not affected by rapid electrolyte and fluid shifts, and can be used to determine blood loss. By subtraction of the postpartum red cell volume from the antepartum red cell volume the apparent loss of red cell volume was determined during this period. (Note: All these determinations had not been done at constant intervals before and after delivery). This loss was then divided by the antepartum hematocrit and multiplied by 100 in order to obtain a figure which approximates the loss of whole blood from the circulation. This formula was used throughout our series of cases. In averaging these figures a surprising correlation is noted. The range of apparent blood loss is from 810 to 1250 ml. It was felt that although the wide variation in blood loss of each individual case rendered the application of statistical verification difficult, proceeding along these lines and confining the studies to the immediate antepartum and postpartum periods, some interesting results could probably be secured.

Standard technics were evolved in our laboratory and they have been described in the article published by Tysoe and Lowenstein.[17] In addition, our complete scientific results have been published in detail.[18] However, there are certain features which should be mentioned relative to their clinical significance.

In our study, 38 cases were divided into three series. The first series of blood volume estimation was completed without informing the obstetrician about the nature of the project. You will note the low visual estimate of blood loss in this first series. During the second series the obstetrician had some knowledge of the plan, and consequently, his visual estimate averaged 103 ml. greater than that of the first series. (Table 2).

It should be noted that there was no appreciable blood volume change between the second and eighth days postpartum. Because of the discrepancy between blood loss

TABLE 2
BLOOD VOLUME ESTIMATIONS

Series A.—14 unselected multiparous cases. (Blood Volume estimates A. P., 24 hrs. P. P. and 8th day)	
Average apparent blood loss by Blood Volume	1031 ml.
Average blood loss by visual estimate	214 ml.
Variation	917 ml
Series B.—14 unselected multiparous cases (Blood Volume estimates A. P., 48 hrs. P. P. and 8th day)	
Average apparent blood loss by Blood Volume	902 ml.
Average blood loss by visual estimation	317 ml.
Variation	595 ml.

estimated visually and the blood volume determination it was decided to measure all blood escaping from the genital tract. This was accomplished by means of an apparatus similar to that described by Carroll.[19] The blood collected in this apparatus was hemolized with water and the amount of blood was determined by the formula.

$$\frac{\textit{Volume of Fluid X Hemoglobin of Fluid}}{\textit{Ante Partum Hemoglobin of Patient}}$$

In addition, the patient's pads were saved and a similar estimate was carried out on the hemolized blood of the lochia.

This series C consisted of 9 patients in whom the antepartum blood volume was determined as close to delivery as possible. The postpartum estimations were accomplished fifteen to ninety minutes after delivery and forty-eight hours later as well as on the eighth day.

Measured blood loss at delivery averaged 224 ml. The amounts of blood lost as lochia during the first forty-eight hours averaged 82 ml., making a total loss of 310 ml. This should be compared to the apparent circulating blood loss calculated by blood volume immediately before and after delivery which averaged 630 ml. This apparent blood loss increased even further to forty-eight hours postpartum to an average of 1041 ml. The discrepancy between measured external blood loss and circulating blood loss as estimated by blood volume studies was 731 ml.

We speculated that this blood was permanently lost to the active circulation and that it was pooled in organs such as the uterus or breasts. Perhaps it stagnated for a long period in the capillary spaces. This recent view is being actively investigated in Boston by Caton and his co-workers using radio-active erythrocytes.

Further investigation must be carried out in this regard but at the present time we may assume that our findings have definite clinical significance. It is undoubtedly true that these cases were able to withstand losses of circulatory blood of the magnitude reported without obvious collapse or shock. However, these 38 cases were all normal, healthy individuals.

Our recent studies show that blood loss at delivery is greater in the anemic woman who has the least blood to spare. Also there are other occurrences which tend to class certain patients as abnormal and create a potential hazard. Spontaneous delivery, well controlled with moderate sedation or anesthesia is conducive to a low blood loss. In contrast episiotomy increases blood loss; and lacerations cause even more hemorrhage. The length of time taken to repair such injuries is sometimes too long especially in the hands of inexperienced individuals. Difficult forceps delivery accompanied by injury to the genital tract is an added risk to hemorrhage and shock. Uterine inertia creating fatigue and dehydration is an associated factor. These conditions may create a state in the patient in which possibly she cannot compensate for the circulation changes, which always occur plus the strain of the additional complication.

Perhaps the most important observation made in our blood volume studies is the following fact. Coinciding with increased measured blood loss at operation or delivery there is a much greater variation in both red cell volume and total blood volume. For example, Table 3 shows 3 of the 9 cases studied in Series C. One individual had minimum blood loss, one was moderate, and the last had the maximum blood loss.

It is noted that in the case with minimum blood loss the discrepancy between measured external loss and circulating blood volume loss to forty-eight hours postpartum was 424 ml. In contrast, the individual with maximum blood loss had a discrepancy for the same period of 1411 ml. This is probably a defense mechanism on the part of nature in a vain attempt to save blood. In the ordinary case it may be advantageous, but in the individual who loses 500 ml. by external hemorrhage one notes that a quantity of blood more than three times this amount of actual hemorrhage is apparently withdrawn from the active circulation. With this occurrence, or if there is some added complication, one can understand the inevitable precipitation of varying degrees of shock.

TABLE 3

Blood Loss	Minimum (ml.)	Average (ml.)	Maximum (ml.)
Measured at Delivery	100)	224)	485)
	)	)	)
	) 168	) 306	) 529
Lochia	68)	82)	44)
Calculated from Blood Volume			
A. P. to 60 min. P.P.	448	630	1580
A. P. to 48 hrs. P. P.	592	1041	1940

Due to the fact that blood loss and shock tend toward hemoconcentration, hemoglobin estimation and the hematocrit are often misleading in the postoperative and postpartum patient. In such cases blood volume studies are beneficial in estimation of red cell volume. Furthermore this affords a more accurate method to measure the indicated amount of blood replacement.

We believe that whenever suitable whole blood is available it should be used to rapidly restore such patients to a normal red cell volume. Most certainly any type of shock is best treated by prevention.

SUMMARY

1. Contributing factors to shock, which include anemia, dehydration, and excessive trauma, should be avoided or promptly treated.

2. Hemorrhage is still the most common condition associated with shock in obstetrical practice.

3. Blood volume changes studied antepartum and postpartum showed a diminu-

tion in the active circulation which far exceeded external measured loss.

4. Blood loss is best replaced by whole blood transfusion.

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ATTEMPTS AT THE CHEMOTHERAPY OF CANCER*

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Attempts at the chemotherapy of cancer are based on leads coming from many directions. They may be divided into, (1) substances which interfere with mitosis, (2) substances which have a greater predilection for cancer cells than corresponding normal ones, (3) cell poisons of various kinds, (4) antimetabolites, (5) naturally occurring substances, such as the hormones.

Discussion of the rationale of each will be given, together with examples illustrating results of their use. None has been found actually curative, but in selected cases palliation has been obtained.

I do not believe it possible to name all the substances or methods of "cure" or alleviation of cancer proposed since the dawn of time, but I do not doubt that they run into the thousands. Most of us actively engaged in cancer work receive plenty of communications from all sorts of sources, amounting in my case to as many as three or four a week, at times. They range all the way from crushed dandelions gathered in the full of the moon to divining rods, thought processes, sleeping with beds running longitudinally from east to west, rather than from north to south, and many others.

The communications come from a variety of persons—from those entirely sincere with a wish to help rid us poor human beings of the dreadful scourge, to those who know better but intend to profit by the gullibility of people and by all the mystery which can be made to surround cancer.

Among these communications, however, others which merit thought and attention are coming from individuals technically trained in other fields who have thought out what they have been able to learn of cancer and have arrived at what, to them, is a rational approach to its conquest. Most of these contain a modicum of what we regard as well established in the subject, but they propose methods which are highly impractical, dangerous, or impossible to achieve, or else they juggle with words and, unknowingly perhaps, present an exercise in semantics. Engineers, chemists, and physicists, for example, who have been successful in fields confined to nonliving substances and problems capable of accurate mathematical analysis, carry over their modes of thinking into the field of living things, including cancer, without the high regard which we who are working with biological material have for the behavior of protoplasm.

Our margins of error in most of the research which we do are such that they are outside of the experience of these people. I often point out to a chemist who has had no experience with living things that when

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*Presented at the Fourteenth Annual Meeting of the New Orleans Graduate Medical Assembly, March 7, 1951.

he pours a reagent from one test tube into a solution to be analyzed he manipulates literally millions of individual molecules and groups, so that his results are statistical approximations of a high degree of probability. When, however, a biologist working with mice performs an experiment he would in truth be happier could he use several million of these animals at one time, so that he too could obtain a statistical approximation of a high degree of probability. But this, of course, is impracticable,—if he uses 500 mice it is a lot. What I am trying to emphasize is that scientific knowledge is composed of approximations and according to the organismal philosophy which is the best for biologists,—and Whitehead says for others too,—an organism is not a sum of its parts and is a system devoid of isolated events. The variability of living things is a primary axiom—not always appreciated in research with living organisms. Ours is an indeterminate world, a concept always held by biologists, and now thoroughly agreed to even by physicists.

I get quite a kick at times by observing the reaction of a chemist or a physicist when he first observes the blood coursing through the capillaries of a frog's web or omentum. If it is a characteristic of matter that it is constantly changing, the rate at which changes occur in living things is a revelation to many who have worked with substances which are "put", so to speak. In life nothing stays as it is for even a fraction of a second, and there are variables without number, most of which we do not even know, let alone are able to control.

All of this is merely a preamble to the statement with which I wish to begin speaking of the attempts at chemotherapy of cancer. In human beings we have so few controls for any particular type of tumor with which we experiment and there is so much variability from case to case that conclusions are, therefore, hazardous in the extreme. All working in this field hope for the kind of conclusive evidence which amounts to observing cancers disappear completely under our very eyes. No one, so far as I know, has observed this as occurring by the use of any chemotherapeutic agent, but has observed only a very occasional approximation to it.

Nevertheless, there are leads in the literature coming from the most varied fields in science, some of which have been followed a short distance. The substances tried may be classified, and the following, I believe, is as good as any:

1. Substances which concentrate in cancer tissue, and thus, specifically bring about changes there and very little elsewhere;
2. Substances which interfere with one of the normal cellular processes such as mitosis;
3. Various cell poisons, general in their action but with a margin toward cancer cells;
4. The antimetabolites;
5. Normally occurring substances which in diminished or increased quantities influence cancer tissues in the direction in which we want them influenced.

To discuss all of these in detail, I am happy to state, would require a large monograph; happy because there has been done a sufficient amount of work and, what is just as important if not more so, a sufficient number of new leads have been unearthed to justify such a monograph. Therefore, I will touch but sketchily upon some, and concentrate on just a few in which we in our institutes and hospitals have had more experience.

SUBSTANCES CONCENTRATED IN CANCER TISSUE

No. 1 in our table, namely, the substances or isotopes of substances which specifically are concentrated in cancer tissue are not known at present with but a few restricted examples. Iodine accumulates in some cancers of the thyroid. The methods used, with that one exception, are those of trial and error. New compounds are made with different internal atomic and group arrangements. I dare say the number is in the hundreds, but this seems to be a very small start. I am told that approximately 30,000 compounds were synthesized and tested before tetraethyl lead turned up as a good antiknock substance for our gasoline. Apparently we have many more to go for the chemotherapy of cancer, unless a great deal

of luck—whatever that is—enters the chemical and biological laboratories.

SUBSTANCES INTERFERING WITH NORMAL CELL BEHAVIOR

No. 2, those that interfere with some part of normal cell behavior, can be exemplified by colchicine. This substance interferes with spindle formation in the mitotic processes. It hinders mitosis at this point, but after twenty-four hours, plus or minus four hours, it lets go. Many of the cells so hindered resume mitosis, sometimes normally, but also sometimes with sticking of chromosomes, doubling or even tripling of them, leading to, shall we call it, mutation. Many of the cells, when their mitosis is resumed are unable to divide again and those perish as far as continuing growth is concerned. But colchicine cannot be used in human beings to interfere with mitosis of tumor cells, not only because it interferes with the mitosis of normal cells, for instance, bone marrow, but also because the dose needed is so large that it produces violent gastroenteritis and general toxic symptoms which often are alarming. Chemists have modified the colchicine molecule and probably over 200 have thus far been tested. Unfortunately, none of these compounds has provided what we want, that is, a substance which will interfere with mitosis, will prevent the cells so treated from further division, and will be but moderately or not at all toxic to the rest of the organism. Other substances with similar properties have also been tested, such as colocynth, but their drawbacks are too serious for use. In short, it is obvious we need much more knowledge of intracellular chemical and physical dynamics for other than trial and error experiments. We know too little of what goes on inside of cells to be able to figure out likely compounds and groups for interference in this type of endeavor.

POISONS

Among those mentioned under *No. 3*, namely, poisons, I cite as examples the nitrogen mustards and the polysaccharides. Experience over the past years has shown that the nitrogen mustards indeed are valuable in the control of a limited type of neoplasm, namely the lymphosarcomas, Hodgkin's disease, and perhaps even leukemias. If they do not of themselves cause regression of the masses they perhaps restore sensitivity to radiation-resistant cases.

The polysaccharides under experiment at the present time come from *Serratia marcescens*. As a direct descendant of the old observation that occasionally a patient with erysipelas and an advanced malignancy recovered from both, Coley's fluids were used. I dare say thousands of patients with advanced malignancies were given these toxins with no result, but every once in a while something spectacular occurred and patients were "cured" of their tumors. Just enough of this happened to continue interest. Then Dr. Murray Shear in the 1920's began fractionating the mixture called Coley's fluid and arrived at a polysaccharide which causes necrosis and hemorrhage in tumors, chiefly sarcomas, in mice, without undue damage to other tissues. He tried them cautiously in human beings and the same phenomena occurred but the polysaccharide preparations were quite toxic. Very graciously asking us to help, we began working with material which he supplied and with his advice five years ago. We find in innumerable mice and about 300 patients that they do indeed produce necrosis and hemorrhage, particularly in sarcomas and to a much less extent in carcinomas. Their intravenous and intramuscular administration produces high fever, chills, and prostration, but at least some of the tumor is destroyed. Definite advantage is had when a hitherto inoperable tumor becomes smaller and more sharply outlined by reason of the ecchymosis, and thus can be removed. Furthermore it often reduces the size of the nodes in lymphosarcomas and Hodgkin's disease and has the big advantage of those which have become resistant sensitive to irradiation.

One drawback is toxicity. Of 100 mice with equal sized and aged sarcomas all can be cured but the mortality is very high and the dosage much greater than is justified in human beings. A further drawback is the rapid immunity which is produced and which hinders continuous administration,

with the idea of destroying small parts of the tumor day by day or week by week until it is all gone. Polysaccharides are extremely complex substances with very high molecular weights. They might be groups of large organic molecules loosely held together as a polymer. The problem is to separate the toxic and immunizing properties of this big aggregation from the tumor-destroying parts. Dr. Creech and his co-workers in our Institute are actually making progress along this line—beginning with polysaccharide 3, known to us at P-3, we now have polysaccharide 30 with fractions numbering into the hundreds. Experiments with tissue culture, with tissues in the Warburg apparatus, and similar technics, indicate that the body metabolizes the substance.

Other drawbacks are the difficulties of producing the material. Various strains of the bacteria are known, and even the same strains do not always produce exactly the same material. Progress is being made, however microscopic or submicroscopic it may be, and in the course of systematic experiments, interesting facts of cell behavior, of immunization, and other processes are emerging.

ANTIMETABOLITES

Probably the antimetabolites are the most interesting at present of the anticancer substances. Theoretically, they are two main types, the one an enzyme antagonist and the other a compound antagonist. Many enzymes are highly specific and if a slight change is made in their composition they no longer attach the compound which the normal one synthesizes or degrades. Compound antagonists are substances which are related more or less closely to normal metabolites but are sufficiently different so that the normal enzymes do not attack them. They thus accumulate within cells and so interfere with intracellular mechanism.

The most used of the antimetabolites are the folic acid conjugates and antagonists. Folic acid is pteroylglutamic acid, and as such is a necessary component of many special intracellular reactions and, following the concept that an organism is devoid of separate events, other mechanisms are secondarily set in motion. Direct analyses have shown that the concentration of folic acid is higher in rapidly growing tissues than in others; thus if cells which are rapidly growing are deprived of folic acid they should perish. Since it is impossible to deprive an animal of folic acid without serious disturbance to the organism as a whole, it was thought that a relative of folic acid could be introduced and perhaps there would be a differential. So two glutamic acids were united to pteroyl acid and three, and four, and a number of others. As a speculation the cell membranes cannot distinguish between folic acid itself and its conjugates called diopterin, teropterin, and others, but once the teropterin is inside the cells the enzymes which normally catalyze the activities of folic acid cannot perform the same function on teropterin and thus the wheels are stopped. Teropterin has been of little if any use objectively in destroying tumors or even inhibiting their rates of growth. It does, however, occasionally improve appetite, maintain a better blood picture, and is of psychological value under the proper circumstances. The use of teropterin in cancer patients, fortunately, has lead to a number of studies of folic acid itself, which to date have revealed nothing startling but merely a number of other problems. Folic acid levels in the blood of normals and of cancer patients are very variable for reasons as yet unknown. Its exact intermediary metabolism, excretion of itself and its products, are all still under investigation.

Further modifications of folic acid consist not only of conjugates but of the introduction of other groups into the molecule. The most important of these is the amino group, which in aminopterin is a potent antagonist. It is highly toxic, must be used with great caution, and will occasionally produce complete regression, especially of acute leukemia in children. It does not cure, but if it does not cause regression it will occasionally transform an acute case into a chronic leukemia which is easier to handle by other means.

A substance called amino-an-fol also contains the amino group, but aspartic acid is present in the molecule instead of glutamic

as in aminopterin. It is less toxic, but in adequate dosage is often just as effective. These antagonists have produced a marked effect upon animal leukemia, have inhibited growth of Rous chicken sarcoma, and have indirect tumor-destroying activity in other forms of animal tumors such as Sarcoma 180 in mice. We have used amino-an-fol to date in 48 patients—none of whom have been cured, most of whom have had no help, but a few have shown some slight destruction in their tumors and perhaps inhibition of rates of growth. The recent introduction of leucavorum (citrovorum) factor as an adjunct has made it possible for us to increase the doses of amnio-an-fol and damp down its toxic effects. We have not as yet seen any results, even with dosages up to 80 mgs. per day.

The number of possible folic acid relatives is large indeed and just enough information has accumulated, practically entirely from animals, to indicate to the chemist a bit more logic for his syntheses than mere trial and error.

The number of possible antimetabolites is limited only by the number of metabolites present in the body, but especial attention must be paid to those metabolites more intimately connected with the growth of cells and in their immediate functions. Thus, as an example, methionine, an essential amino acid, contains the methyl group. Replacements with the ethyl group result in ethionine. It is possible to make butylthionine, amylthionine, and the whole list of hydrocarbon groups. The same is true of the pyrimidine metabolites or more directly the nucleic acid substances. Obviously the syntheses should be based upon our knowledge of general intermediary metabolism and hence, among other reasons, the importance of this subject in cancer research.

SUBSTANCES NORMALLY PRESENT IN THE BODY

Among the substances normally present in the body of known effect on cancer, we will confine remarks to several of the hormones with the understanding that other substances such as enzymes and vitamins also may be classified under this heading.

The exception I mentioned above in speaking of specificities is the thyroid gland with its proclivity for seizing iodine. Not all cancers of the thyroid gland store iodine, only those with cells containing laboratories within them which can pick up iodine and use it. In pathological terms they are adenocarcinomas of the thyroid. The rationale of the use of radioactive iodine is thus to be explained.

The outstanding example of the effect of hormones upon cancer is provided by cancer of the prostate. Large metastatic deposits disappear in many cases upon removal of the testes. Perhaps less effective, but there is debate on this point, are the female sex hormones which also when given in large doses cause regression. As a speculation with some foundation in fact, the following mechanism may be postulated: The maintenance of differentiation of the cells lining the acini of the normal prostate is dependent upon testicular secretion. If this is removed atrophy results. If a cancer of the prostate has many highly differentiated cells (producing acid phosphatase) that is, if it is an adenocarcinoma, the differentiated cells in the tumor likewise are maintained in their state of differentiation by testicular secretion. If this is removed or overwhelmed by female sex hormones those cells of the tumor which were dependent upon testicular secretion undergo atrophy and disappear. Thus are the masses removed. Naturally this broad-jump theory is not as simple as it sounds, but in another communication I am discussing more in detail the differentiation problem.

It is said that in the handling of metastases from carcinoma of the breast male hormones should be used in patients under 50 and female hormones in those over 50. The debate upon this point, however, is hot and heavy. Sufficient evidence has accumulated that a few persons receive marked benefit from the administration of the male hormones, but further experience also shows that some, no doubt fewer in number, are benefited by female sex hormones. Correlation between physiological activity of the tumor cells and their dependence upon female and/or male hormones, has not yielded unequivocal results.

As a matter of practice, however, it is our habit to first try large doses of male hormones, and then, if no distinct benefits occur, or if what benefits have been observed cease to be progressive, to switch to female sex hormones. It is only fair to state that in a few of our patients both have had an effect opposite to that wanted, namely, have seemed to accelerate the rates of growth.

RESULTS

From the above it is obvious that no chemical cures for cancer have been discovered, but it is also encouraging to know that real attempts are being made in this direction. All of us are asked the question, if not in this form at least in one similar to it—"How soon do you expect you will discover a 'cure for cancer'?" My reply is that I am no prophet. How can I tell when something is going to be discovered, and what? If I knew the answer I would quit working on the subject and tackle another. It is true that from laboratory success to pilot plant to actual production can be timed with some accuracy in certain fields, especially in commercial work. It is also true that the more manpower is placed upon such a set-up the less time until results are obtained. But this has little application when discoveries are wanted. Mere manpower is not sufficient. Discoveries are in a different category than inventions—and what we need in cancer are more discoveries.

I cannot fail to point out what it means to carry on an extensive program to find substances of chemotherapeutic usefulness in any field, let alone cancer—as so ably carried out in several laboratories, notably in New York. Here is what is necessary: Chemists as a rule can synthesize numerous substances while the biologist is still testing one. Tissue culture is needed, of both normal and tumor cells. Various types of living organisms in the growing stages, chick embryos, plants, unicellular organisms, bacteria, yeast, fungi, mice, rats, rabbits, and others are essential tools. In the case of mice—any old mouse will not do. Genetic background must be known, large numbers must be bred and maintained. Tumors must be transplanted or animals inbred until they appear spontaneously, or by the use of carcinogens. Adequate control animals must be provided. A substance under test must be assayed for dosage, for toxicity, and for potency in destroying tumors. The entire animal must be autopsied, both gross and microscopic examinations made, the controls carefully compared, and finally the results of all of the various experiments critically assayed. I leave it to you to visualize the organization necessary for such work.

I am sorry I am unable to present you with results more definite, not to say dramatic, but this is really a progress report,—microscopic progress, or submicroscopic if you will, but nevertheless some. I submit it to you with the hope that you will encourage those of us in this work, will appreciate the difficulties, and will help us where you can.

A CARDIAC COMPLICATION OF SERUM SICKNESS

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NEW ORLEANS

Occasionally the opportunity of seeing one of the rarer disease states or syndromes presents itself to most physicians. Their recognition can be made more readily possible if those who see them bring them to the attention of the profession.

It is the purpose of this paper to report an interesting, as well as an unusual cardiac complication of serum sickness. That this condition is unusual is attested to by the fact that in a survey of the literature over the past twenty-five years, only 6 cases are reported in which cardiac complications developed following the administration of tetanus antitoxin. There are a few more similar cases reported following the use of other therapeutic agents such as penicillin, typhoid vaccine, arsenicals, and aspirin; and with sensitivities to certain antigens such as milk and sea foods.

Three of the previously reported cases following the use of tetanus antitoxin developed myocardial infarcts, 2 cases are re-

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ferred to as myocardopathies, and 1 developed angina pectoris.

CASE REPORT

Mrs. H. L., a 29 year old housewife, received a puncture wound of the plantar surface of the right foot on June 21, 1950. On the same day she was given 1500 units of tetanus antitoxin two hours after trauma. On the night of June 28, at about 9:00 p. m. She began to note itching of the skin and in the course of a few hours she had a generalized urticaria. At about 3:00 a. m. the following morning she noted severe weakness and inability to stand. Her husband, who is a physician, administered 50 mg. of pyribenzamine at which time her pulse was described as being rapid and thready. Associated with the above symptoms she experienced severe retrosternal pain distributed between the xiphoid process of the sternum and the upper portion of the neck. About one hour after the administration of the first dose of antihistaminic, the rash faded, itching was no longer bothersome, and the pain disappeared. However, the effect lasted for only two hours when all the above symptoms returned, and in addition, she developed weakness. Again the same antihistaminic was given and relief was obtained as before. At no time did she have fever or joint manifestations. The review of systems offered no additional complaints.

In the past history she had had no serious illness; however she had received tetanus antitoxin two and a half years previously. There was no past history of diabetes, syphilis, hypertension, or myxedema.

In the family history one sister had hay fever and a brother developed peripheral nerve palsy complicating the Pasteur treatment.

The positive physical findings were a healed puncture wound of the plantar surface of the right foot, severe generalized urticaria, and a regular tachycardia of 120 per minute. The blood pressure was 110/70. There was no evidence of arteriosclerosis, either in retinal vessels or peripheral arteries. The following laboratory data were obtained: Kolmer and Kahn were negative. The blood sugar was 96 mg. %, cholesterol 175 mg. %. The first electrocardiogram (Fig. 1) performed on June 29 while she had urticaria and pain, revealed an isolectric T1, inverted T2, T3, Tv4, Tv5, and Tv6. After the initial electrocardiogram she was placed on 50 mg. pyribenzamine every two hours, whereupon the urticaria and chest pain disappeared, never to return. Serial electrocardiograms taken at twelve hours after the first one (Fig. 2), at three days (Fig. 3), and six weeks (Fig. 4) all reveal progressive improvement to the extent that in three days the electrocardiogram may be interpreted as normal.

In reviewing the various contributions on this subject, Longcope,[1] in 1915, demonstrated by means of animal experiments extensive degeneration of muscle fibers of the myocardium following repeated injections of foreign protein after these animals had been sensitized. Boughton,[2] in 1917, found by injection of foreign protein in sensitized guinea pigs that he could produce lesions of the coronary vessels characterized by edema of the intima, degeneration of the endothelium, edema of the media, and sometimes splitting of the internal elastic membrane. Clark and Kaplan,[3] in 1937, studied the tissues of individuals who had serum sickness from antipneumococcal serum, but who had died of other causes. In some of

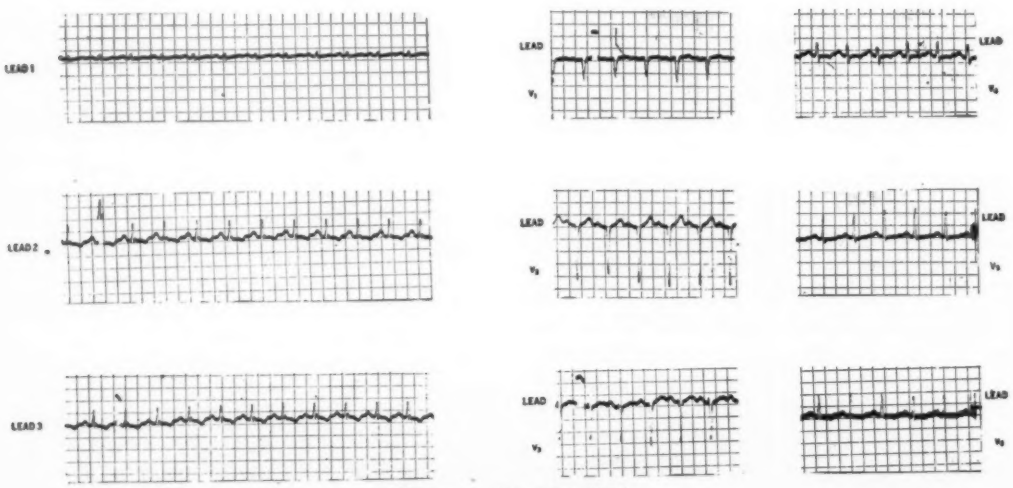

Figure 1—June 29, 1950

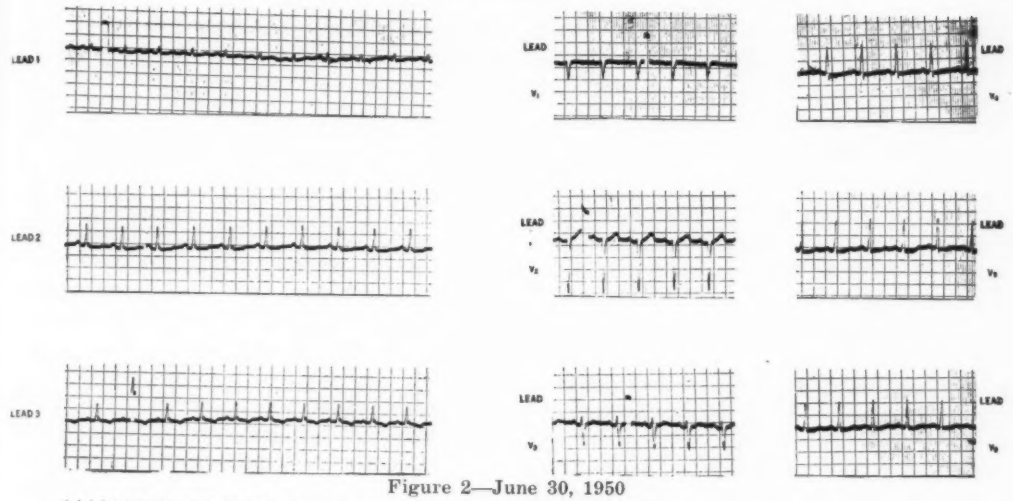

Figure 2—June 30, 1950

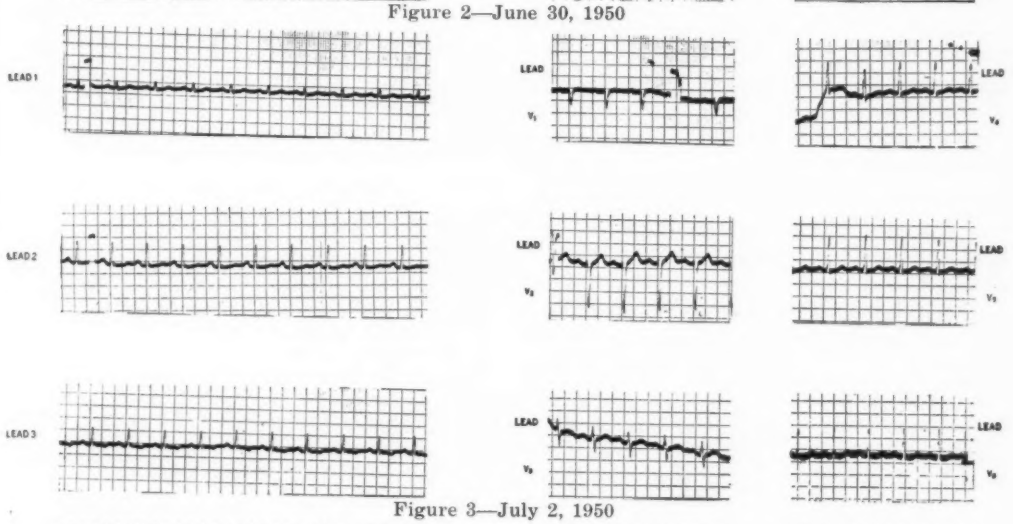

Figure 3—July 2, 1950

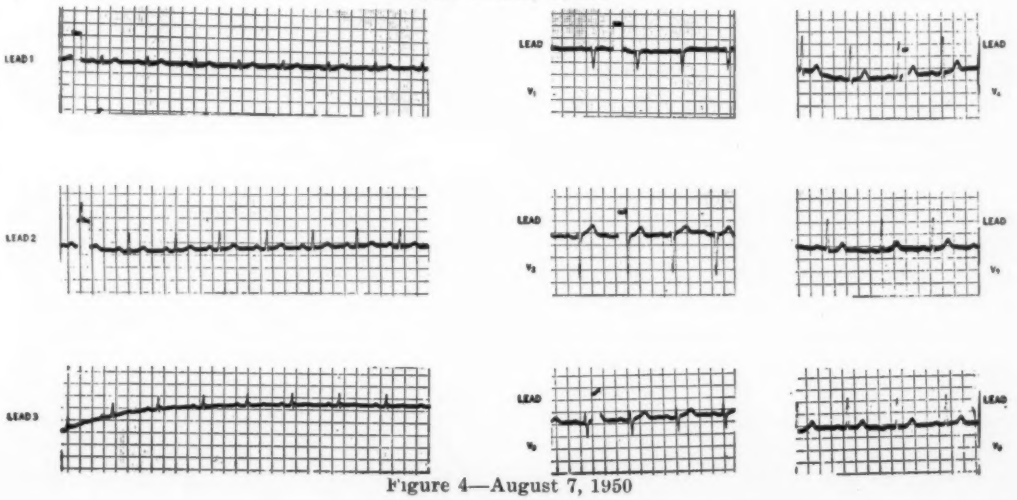

Figure 4—August 7, 1950

these cases they were able to find in the endocardium, the interstitial tissue of the myocardium, liver, kidneys, adrenals, aorta, and pulmonary artery, proliferation of histiocytes, infiltration of lymphocytes, eosinophils, and focal areas of edema. In some of the vessels of the myocardium there were areas of focal periarteritis, areas of subendothelial proliferation of histiocytes, necrotizing arteritis, and sometimes swelling and fragmentation of collagen fibers of the vessels. Wilcox and Andrus,[4] in 1938, were able to show in guinea pigs and rabbits that anaphylaxis could produce a delay in auriculoventricular conduction, changes in QRS configuration of the electrocardiogram, ectopic arrythmia and striking reduction in coronary blood flow. Arnold Rich,[5] in 1942, studied cases similar to those of Clark and Kaplan and was able to find in the tissues fresh vascular lesions characteristic of periarteritis nodosa. Rich and Gregory,[6] in 1943, produced a hypersensitivity state in animals by prolonged repeated contact with an antigen and were able to find in the blood vessels lesions analogous to the cutaneous anaphylactic wheal. The vascular lesions were characterized by the accumulation of edema fluid and inflammatory cells beneath the endothelium of affected arteries. Often actual necrosis of the endothelium developed. The localized areas of edema in some of the arteries seemed to separate the muscle fibers of the media and some of these muscle fibers had undergone necrosis. Rich and Gregory suggest that the lesions represent in effect "hives" of the blood vessels analogous to the cutaneous reaction of serum sickness. Kyser, McCarter, and Stengel,[7] in 1947, duplicated the work of Rich and Gregory but, in addition, were able to prevent the development of the vascular lesions if the antigen was given along with benadryl.

From a review of the literature credit for the first reported case of angina complicating hypersensitivity reaction goes to Lichtwitz,[8] who first associated the two conditions in 1925. Werley[9] next, in 1932, reported a case of anginal syndrome with electrocardiographic changes associated with angioneurotic edema. Shoakoff and Lieberman[10] report in 1933 the association of the anginal syndrome and urticaria following the ingestion of aspirin. In this case, attacks could be produced at will by the administration of this drug. Von Eiselsberg,[11] in 1934, reported repeated episodes of angina with hypersensitivities to certain foods. By means of elimination diet and the avoiding of certain offending food allergens he was able to prevent recurrences of anginal attacks. Wadsworth and Brown,[12] in 1940, reported a severe serum reaction in an 11 year old boy, complicated by an acute and chronic carditis. The patient developed tachycardia, tick-tack rhythm, gallop rhythm, and an electrocardiogram characterized by slurring and widening of the QRS complex. Fox and Messeloff,[13] in 1942, presented a case in an 18 year old boy, who following tetanus antitoxin developed urticaria, angioneurotic edema, and marked QRS and S-T segment changes. Mathieu and Hadot,[14] in 1947, reported one case of serum sickness complicated by anginal syndrome and another complicated by posterior myocardial infarction. Felder and Felder,[15] in 1950, presented a case in which a penicillin in oil reaction was characterized by giant urticaria and who on routine electrocardiogram showed QRS and T wave changes which reverted to normal one week after the urticaria had subsided. This patient had no chest pain. Again in 1950, McManus and Lawlor[16] reported a serum reaction in a 32 year old male complicated by the development of a posterior myocardial infarction.

DISCUSSION

This case in a young adult female represents an unusual reversible form of heart disease. Absence of diabetes mellitus, myxedema, arteriosclerosis, hypertension, syphilis, infection, severe anemia, and hypercholesterolemia precludes the possibility of some of the commoner responsible factors in the etiology of heart disease.

That the retrosternal pain became apparent only when the skin manifestations were pronounced, and waned with the fading of

the skin eruption on several occasions, suggests that lesions in the heart comparable to those of the skin must have been present. The abnormal electrocardiograms obtained at the height of the skin manifestations and during pain with its gradual return to normal tend to support this contention.

The mechanism by which this cardiac picture developed in this patient is suggested by the experimental and pathological studies done by Boughton, Rich, Gregory, Clark, Kaplan, and others. Their work would seem to indicate that there must have been a reduction of coronary blood flow and resulting hypoxia of the myocardium. This reduction in blood flow must have been due to a reduction in size of the lumen of the coronary vessels as a result of edema and inflammatory cells beneath the endothelium and in the media. Such lesions may be analogous to cutaneous urticaria.

SUMMARY

A case of serum sickness complicated by anginal syndrome with electrocardiographic changes is presented. The mechanism by which this cardiac complication developed is discussed.

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MANAGEMENT OF RECURRENT ABRUPTIO

REPORT OF A CASE

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Cesarian section is not a routine in the management of abruptio placenta but is done in select cases in the interest of the child and/or the mother. Many pregnancies with this complication end favorably vaginally. Section is indicated in severe cases when the mother's life is jeopardized by toxemia or shock, and termination by the vaginal route is not feasible. It is also done in the occasional progressive case in which the life of the fetus depends on rapid removal, and section is the route of choice. Placental separation is one of the most common causes of premature labor and is the most common cause of last trimester bleeding.

Abruptio placenta is defined as premature separation of a normally placed placenta. It may be divided into three types: minor, moderate, or severe, depending on the amount of separation that exists.

In most severe abruptios the fetus is dead when the patient is first examined. While shock is being combatted an aseptic vaginal examination is performed. If on examination the cervix is found to be partially taken up and slightly dilated, and provided shock can be successfully treated, rupture of the membranes in conjunction with small doses of pitocin may be used to initiate good labor or hasten labor if such has already developed. On the other hand if the uterus is contracting poorly, in a semitetanic state, and the cervix canalized, then delay would jeopardize the mother. However, one could elect to observe such a case if the general condition was good, as many will soon go into active labor and deliver from below. Each case has to be individualized. Adequate blood should be on hand and the operating room ready.

Fortunately, the majority of placental separation is of a minor degree and no active treatment is necessary for this type.

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In between these groups of severe and minor is placed moderate abruptio. Practically none of this class will require section for maternal cause but a few operations will be necessary for fetal indications. Again this would depend on cervical dilation, amount of hemorrhage, primiparity, multiparity, and number of weeks gestation. Few obstetricians would section only for fetal indication, a pregnancy which is no further than thirty-two weeks' gestation.

The patient under discussion had a very unusual obstetrical history. In seven pregnancies she had four, or possibly five abruptios. In only one of seven consecutive pregnancies did she carry beyond thirty-four weeks and this was the only pregnancy in which stilbestrol was continued beyond the thirty-second week. It is also of interest that severe abruptio occurred just two weeks after cessation of similar therapy in the sixth pregnancy. In only the last two pregnancies were adequate doses of stilbestrol given and the course of these pregnancies compares favorably with the other five.

It is doubtful as to whether progesterone was of any value in the successful outcome of this case since the dosage was quite small and was taken orally. Estrogenic therapy in the treatment of threatened abortion is open to considerable question. Its use, however, prophylactically in the chronic aborter and in late pregnancy complications seems, at the present time, to be of some value.

The purpose of this case report is to present a plan of management of the occasional case of recurrent abruptio and to lend support to the value of high doses of estrogenic therapy in the treatment of late complications of pregnancy.

CASE REPORT

Mrs. A. G., 31 year old G7, P3, Ab3, was first seen in her thirtieth week of gestation following transferal from another naval hospital. Despite her parity she had one living child as one of her infants had been stillborn and another died soon after birth.

General physical examination and past medical history were not significant.

Obstetrical history was quite remarkable. In 1940 and 1941, she had two spontaneous abortions. In 1942, she had a moderately severe abruptio with spontaneous delivery of a viable male infant—birth weight 5.1 pounds—which survived the neonatal period. She was divorced shortly afterward and did not remarry until 1947. She promptly became pregnant and during her first trimester experienced slight vaginal spotting and was placed on minute doses of stilbestrol. During her thirty-first week of gestation she awoke with severe abdominal pain and vaginal bleeding and spontoneously delivered shortly afterward a viable premature infant that lived only a few hours.

In 1948, she became pregnant for the fifth time and was placed on oral stilbestrol and parenteral progesterone (exact dosage not known) despite which she miscarried at four months.

Her sixth pregnancy occurred in 1949 and she received 50 mgm. of stilbestrol orally and 25 mgm. of progesterone twice weekly by hypo beginning early in the first trimester. Her prenatal course was uneventful and therapy was discontinued at thirty-two weeks. Exactly two weeks later she experienced severe abdominal pain accompanied by vaginal hemorrhage. On admission to the hospital the baby was thought to be dead and she was allowed to deliver spontaneously some eight hours later. The infant was stillborn. This abruptio was associated with a sudden onset of toxemia which promptly subsided soon after delivery.

By this time the patient was extremely apprehensive at the thought of future pregnancies although she was particularly anxious to have a child by her present husband as her only living child was from her former marriage.

Despite contraceptive measures she became pregnant soon after. In her eighth week of gestation she experienced painless vaginal bleeding and was placed on 50 mgm. oral stilbestrol daily and 10 mgm. pranone parenterally twice weekly.

She reported to this facility for the first time in early March 1950 in her thirtieth week of pregnancy. Pranone was discontinued at thirty-two weeks. In view of her past history she was admitted to the hospital at the beginning of her thirty-third week.

Plan of management consisted of continuance of the stilbestrol (Smith), close observation for any evidence of abruptio and in that event immediate section, otherwise elective section at eight months.

Her hospital course was uneventful until one morning in the early part of the thirty-fifth week she experienced pain in the right lower quadrant of the fundus which was accompanied by a small area of tenderness in the same area. Diagnosis of a small infarct was made and a low longitudinal section was performed shortly afterward. A viable female infant—weight 5.3 pounds—was delivered and examination of the placenta confirmed the clinical impression of the infarction.

Mother and infant left the hospital on the sixth post partum day following an uneventful postoperative course.

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SCHWANNOMA

A CASE REPORT

JOSEPH COHEN, M. D.

NEW ORLEANS

This tumor is rare, and no case like it was found in the archives of Charity Hospital or Touro Infirmary, or in the literature available to me. It has in addition some other unique features, and therefore, merits reporting.

A schwannoma is an encapsulated nerve sheath tumor, arising from the cells of Schwann. The tissue is highly differentiated; the cells having elongated nuclei and are either arranged side by side to resemble palisades or grouped with fibres to look like whorls. The tumor as a rule is soft in consistency, often cystic, very vascular with dilated capillaries and sometimes thrombosed vessels, with dense collagen sheaths around the blood vessels, and frequently containing old blood pigment and hemorrhage.

This tumor has been classified and named differently by various authors: Penfield believed it had a connective tissue origin and called it perineural fibroblastoma. Verocay[14] thought histologically it was of nerve fibre origin and called it neuroma; whereas Masson claimed it originated from the cells of Schwann and called it schwannoma. Haeckel refers to it as lemmona. Roussy, Libermette and Cornill consider the cells of Schwann as neurologic cells and call it peripheric glioma. Stout[11] agrees it is a nerve sheath tumor and calls it neurilemmoma and makes a very careful distinction between it and neurofibroma, a catch-all term erroneously applied frequently to the type of tumor under discussion.

The schwannoma develops in the perineurium and as it grows the perineurium expands and forms its capsule, the nerve bundles never being found inside of the tumor capsule. The capsule is often well supplied with blood vessels.

Whether the tumor produces symptoms depends on the importance of the nerve trunk involved and the degree of involvement; therefore, in many instances it may prove to be a painless, symptomless tumor. Rare cases have been reported of finding the tumor in the gastrointestinal tract attached to the stomach or small intestines, and discovered at exploratory operations or autopsies.

Christopher,[3] in 1945, classified 2,505 gastric neoplasms and did not find one case. Ensterman and Senty,[4] in 1922, did not find one in 2,168 nonmalignant neoplasms. Arthur Purdy Stout,[11,12] in 1935, examined all evidence of previously reported gastric tumors of neurogenic origin and accepted 32 as true nerve sheath tumors and added 3 cases of his own. Sjorall in 1937 in 31,331 autopsies found only 2 in the small intestine. Hoffman & Grayzel,[5] in 1945, reviewed 64,300 surgical specimens and 4,480 autopsies and found 33 benign tumors of small intestines and only 1 had fibroma-like characteristics.

The neck is the usual site, and the tumor comes most commonly from the cervical plexus. It has been found attached to the spinal nerve roots and to the intracranial portions of the cranial nerves, as well as the nerves of the extremities.

This tumor is found in both sexes and in

Presented at meeting of the Orleans Parish Medical Society, December 11, 1950.

all age groups; is not caused by trauma and is usually slow growing; is not malignant and can be completely excised.

CASE REPORT

The patient, a white, 29 year old female was sent to me on July 16, 1949, because of an enlarged left submaxillary gland. She had measles as a child, an appendectomy in 1936 and a very normal menstrual history beginning at 12, four to five days duration, twenty-eight day cycle, without any dysmenorrhea. Married eight years, she had a two year old child, and no other pregnancies. She ate well, slept well, had daily evacuations and no urinary disturbance.

Physical examination disclosed a large left submaxillary gland about the size of a walnut. A stone in Wharton's duct was suspected and proved by subsequent x-rays. Her blood pressure was 110/72. Heart and lungs negative. Reflexes normal. Good abdominal muscles and an appendix scar were present, with no abdominal tenderness. Vaginal examination revealed a large smooth globular mass, nonmovable, frozen to the pelvic floor, about the size of a grapefruit. The cervix was slightly lacerated and tipped anteriorly. The perineum had a first degree laceration. The adnexa could not be mapped out, nor could the uterus be outlined. The condition was thought to be chronic pelvic inflammatory disease with a globular mass in the center. Rectal examination permitted the index finger to get under the mass but it was immovable and painless. A diagnosis of pelvic inflammatory disease with an intramural fibroid was made and surgery suggested.

The patient desired another child and could not understand the cause for her secondary sterility. Both she and her husband had to be prepared psychologically for the loss of one or more of her generative organs and for the possibility of no further children.

On August 10, 1949, under spinal anesthesia (nupercaine) a midline incision was made and the abdomen opened. The omenteum was adhered to the anterior abdominal wall. It was dissected free. On visual examination the pelvic organs could not be seen due to the mass of adhesions giving the impression of a "frozen pelvis." The adhesions were delicately dissected free. The rectosigmoid was liberated and isolated, and under all this was then found a small uterus and apparently normal looking tubes and ovaries which had enveloped themselves around and accepted the outline of a retroperitoneal tumor that apparently was attached to the sacrum and coccyx and filled the hollow.

The first impression was that we were dealing with a fibrosarcoma or sarcoma. The pathologist was sent for and the posterior peritoneum opened. A wedge-shaped piece was removed for a rush diagnosis. The pathologist reported that the tumor simulated a neurilemomia or Schwannoma.

There were many small and large tortuous vessels on the periphery of the tumor. Lines of cleavage were looked for and after meticulous dissecting, the tumor itself, which was found to occupy the hollow of the sacrum and to be associated with the sacral plexus, was dissected free and enucleated in toto. All free bleeding points were ligated, the posterior peritoneum sutured and the abdomen closed in layers.

The pathological report was as follows:

Specimen consisted of an oval mass shaped like an orange measuring 8 by 7 by 6 cm. covered with a thin white capsule covered with many areas of hemorrhage varied in color from dark brown to bright red. The surface of the tissue was dotted by many round small yellow projections which varied from about 5 to 15 mm. in diameter and were about 2 to 3 mm. above the surface. These areas were firmly bound to the tissue around and beneath them and did not move easily. These nodular areas were harder than the surrounding tissue in some places and in some areas softer. The capsule stripped fairly easily from the mass it enveloped and was fairly firm, tough, grayish white fibrous tissue which measured about 1 mm. in thickness. Cut sections revealed many areas lemon yellow in color and somewhat circumscribed and nodular. The intervening tissue tended to be nodular. Bounding these lemon yellow areas were thin areas of grayish white tissue which were very firm. The rest of the surface was made up of some grayish yellow tissue which was fairly soft and well demarcated. There were no cystic areas. At one end of the specimen were seen several areas of hemorrhage.

Microscopic: Sections showed the tumor mass to consist largely of cells whose nucleus was small and spindle-shaped. They formed fasciculated bundles with their cells running in all directions. Areas showing degeneration and foam cells were present.

Diagnosis: Neurilemmoma (neurinoma, Schwannoma).

M. SUGAR, M. D.

Her postoperative recovery was uneventful except for a pain in the right big toe and cramps in the right foot, which were relieved by rubbing the calf of her leg and which gradually disappeared. I am happy to report in addition that she is pregnant now and expects her baby about the middle of February.

CONCLUSION

In conclusion—this case teaches us:

1. That a complete physical examination should be made on all new patients.

2. That once the abdomen is opened, a biopsy should be done no matter how malignant a tumor appears to be.

3. That a large symptomless retroperitoneal tumor can be present in the hollow of the sacrum.

4. That it can be a benign schwannoma attached to the sacral plexus.

5. That it can be enucleated in toto without any permanent damage to the patient.

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TULAREMIA TREATED WITH STREPTOMYCIN

ANALYSIS OF FIFTY-FOUR CASES

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NEW ORLEANS

This series reports 54 cases of tularemia treated with streptomycin between January 1, 1946, and January 15, 1950, at the Charity Hospital of Louisiana in New Orleans. Of these, 25 patients were of the white race and 29 colored. Thirty were males and 24 females. The ages ranged from six years to seventy-two years, with an average of thirty-nine. Forty-four cases were the ulceroglandular type, of which 38 had the primary lesion on the hand. There were 4 cases of the glandular type, 3 of the typhoidal, 1 oculoglandular, and 1 combined anginal and typhoidal. The incubation period varied from one to possibly seventeen days, with an average of four days. (The history in many cases was inadequate.) Rabbits are the main animal vectors in this part of the United States, as they accounted for 44 cases of this series. Ticks caused infections in 4 cases, the remaining 4 cases having an unknown or indefinite contact.

Presented at meeting of the Orleans Parish Medical Society, February 13, 1950.

Agglutinations were not positive in every case reported in this series, but where they were not diagnostic, only those cases are reported whose history, clinical findings, and clinical response conform to a clinical diagnosis of tularemia. Also, in each of the latter cases the agglutination tests had been taken in the first two weeks of the disease, when we would expect negative results anyway. One exception is present, however, in the instance of a husband and wife who came in at the same time, having the same symptoms and clinical course and response to therapy. After twenty days the wife's agglutinations were negative, but the husband's were positive 1:640. Another husband-wife infection also occurred.

The earliest day a positive agglutination titer was found was the ninth day, although a titer of 1:40 was found on the second day in one case. There was one case with a titer of 1:40,960. One case not treated with streptomycin had a titer of 1:50,880; and one titer in this series (not confirmed by laboratory records) was 1:163,840. A titer of 1:80 or 1:60 was considered diagnostic. There are 5 cases which are examples of patients who do not respond to the infection with adequate antibody levels. These are the patients whose lives are saved by early streptomycin therapy. One case was treated too late in the disease, and death ensued.

Another case is interesting in that he had a history of "rabbit fever" six years before the present infection. One infection is reported as giving lifelong immunity.

Development of agglutination titers was delayed in 3 cases. As long a delay as forty-three days has been reported.[1]

The complications seen were: pneumonia (14 cases), skin rash (6 cases), enlarged liver and spleen (5 cases each), pleural effusion (4 cases), cerebral findings from meningismus to coma (4 cases), pharyngitis (3 cases), lung abscess, acute psychosis, cystitis, and empyema (each 1 case). Twenty-six cases had no complication.

The total amount of streptomycin given varied from 0.1 gram to 64.0 grams. The

average total dose was 14.4 grams. An average of 1.46 grams per day were given in these cases, in an average 11.67 days. The 2 to 3 grams of streptomycin recommended as a total dose by Foshay[2] seems too small, even in uncomplicated cases. About 6 to 8 grams total dose should be necessary. It was noted in this series that it mattered little by what dosage schedule the streptomycin was given, as the response was similarly good in all cases. However, 1 gram per day for four or five days, then ½ gram per day for three or four days in two to four divided daily doses, seems to be the correct dosage schedule. In several cases seen late in the disease, streptomycin was used only in small doses (¼ gram or less) introduced into fluctuant nodes after their aspiration. This therapy proved of no value.

Other conditions present during the illness did not seem to influence the course or effects of the tularemic process except in 2 cases. Both of these had diabetes mellitus and were gravely ill. One case did not survive.

Streptomycin was started from one to sixty days after the onset of the illness. The average was 14.2 days. As a rule, the earlier streptomycin was started, the shorter was the active phase of the disease, the shorter was hospitalization time, and the fewer were complications. If streptomycin therapy is started within the first seven to ten days, the clinical response is dramatic. If started later, the response is quite satisfactory, but short of dramatic.

There was in these cases, an average 3.5 days morbidity after starting streptomycin, with a range of one to nine days. This certainly shows the therapeutic efficiency of streptomycin in tularemia.

Hospitalization time after onset of streptomycin therapy was, in this series, an average of 16.4 days, with the range from 3.5 to 49.0 days. In the author's opinion most of the time was wasted and was used in watching fluctuant nodes and pulmonary lesion resolution. The latter gradually resolve with time anyway. Occasionally, (with meningoencephalitis, empyema, or perhaps lung abscess) a patient may be allowed a long convalescence, but in the ordinary case, they should be discharged to home care seven to ten days after symptoms have abated.

No case of streptomycin toxicity was noted in this series, but this report is not reliable, as specific and/or regular vestibular and other tests were not done.

Not one culture in this series was positive, as the specific blood-glucose-cystine agar was not used. Neither animal inoculations nor intradermal skin tests were used.

The condition of the lymph nodes on discharge was unknown in 19 cases, healing in 13 cases, and still fluctuant in 12. Incision and drainage, which is the treatment of choice, was not used in this series. One case had the nodes excised, however.

Only two deaths occurred in this group. The first had therapy started on the thirty-first day of the disease. In addition, pulmonic and cerebral complications which were present were the deciding factor in this case. The second case also had therapy started relatively late (ninth day) in the disease and an uncontrollable diabetes mellitus with its associated complications caused death. The mortality rate in this series, then, is 3.7 per cent.

SUMMARY AND CONCLUSIONS

1. Streptomycin is the treatment of choice at present for all types of tularemia.

2. Streptomycin should be given on clinical suspicion of the disease, even before serological proof can be obtained. In this way, morbidity time and hospitalization time can be shortened, and mortality rate lowered. In this series, the two deaths had streptomycin started too late to avert fatal complications.

3. The dosage of streptomycin is advised.

4. Fluctuant lymph nodes should be treated by incision and drainage. Resolving pneumonia should be treated by observation. Neither should increase hospitalization time.

ADDENDUM

Since the manuscript of this paper was completed the outlook of chemotherapy of tularemia has changed. The drug aureomycin has become more plentiful and more

cases of tularemia have been treated with it successfully. Two advantages it has over streptomycin are its efficiency by the oral route of administration and its lack of toxicity to the ear. Enough cases have not yet been treated to determine the superiority of one or the other drug, but both are highly effective in the chemotherapy of tularemia.

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LOWER LOBE TUBERCULOSIS*

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AND
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NEW ORLEANS

The special problem concerned with primary lower lobe tuberculosis has been receiving attention periodically in the medical literature for many decades. Usually, renewed interest is provoked by the introduction of different therapeutic technics or different pathogenetic concepts. Such is the situation now when pneumoperitoneum and surgical resection have raised the question of proper management. We have reviewed our 7 studied cases of primary lower lobe tuberculosis and shall attempt to present the part played by lower lobe disease in the over-all picture of pulmonary tuberculosis.

PATHOGENESIS

The pathogenesis of primary lower lobe tuberculosis is unsettled, just as is that of upper lobe disease. Many different viewpoints have been expounded in the literature. Probably, most orthodox is the concept based on the anatomical proximity of the lower lobe and upper lobe disease.[3, 5] Large scale observation reveals that lower lobe tuberculosis always starts in the superior segment (apex) of the lower lobe. This is usually obvious in an early localized process and is to be found in most of our cases. After progression of the disease, however, the process usually spreads to the more basal portions of the lobe, and so the original site of onset is obscured.

The superior segments of both lower lobes lie mostly in the posterior plane, in the paravertebral region. This region is immediately proximal to the most common site of involvement in pulmonary tuberculosis, the posterior subapical area of the upper lobe. Thus has arisen the belief that the posterior portion of the cranial one fourth of the lung has a particular pathophysiological predisposition to the development of pulmonary tuberculosis and this zone extends down far enough to include the apex of the lower lobe.[3, 5]

Numerous studies have tended to support the frequency of pulmonary tuberculosis in this described area. Sweeny, *et al.*,[9] have made a study of the primary tuberculous cavity. They have shown a very great trend toward the posterior location of primary or early tuberculous cavities, all falling into the anatomical zone described. By primary tuberculous cavity they refer to the original focus of reinfection type of tuberculosis, the "mother lesion".

There are several physiological forces that are mentioned from an etiological standpoint as significant for this predisposition. Stressed are the minimal variations in respiratory volume in this region, for this area is partially surrounded by rigid thoracic structures.[3] Advanced, also, as a physiological basis is a study of diaphragmatic[5] motion. The diaphragm is thought to expand mostly that portion of the lung below the fifth rib, with most tension exerted on the lateral lung portion. The remainder of the lung is acted on mostly by the costal mechanism. The lower lobe apex is in a borderline zone where the effectiveness of diaphragmatic motion would determine its respiratory expansion. The

*Presented at meeting of the Orleans Parish Medical Society, November 13, 1950.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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strikingly higher incidence of lower lobe disease in women is attributed to the fact that female respiration is predominatly costal.

Whether this mechanical concept has much weight remains to be proven. The more recent interesting concept[2] that explains the pathogenesis of apical disease on the basis of decreased circulatory pressure differential in the erect human can be used to supplement these thoughts. Integrating all of these concepts would help to explain lower lobe disease, for, by itself, Dock's idea on circulation does not help us understand lower lobe disease, but it can supplement the etiological factors causing upper lobe disease.

There are other sources that have found support, for example, that lower lobe disease may be an atypical manifestation of hematogenous tuberculosis. Actually, this does not represent a different concept, but rather explains the more basic step, that is, that adult tuberculosis is due to reactivation of a lesion that was started during the hematogenous dissemination that occurs as part of primary disease. The reason for activation of hematogenous focus in a superior segment rather than in the upper lobe can be explained by the preceding. In fact, the usual type of progression in miliary tuberculosis of the lung is also to be explained by these preceding thoughts. Clinical experience supports the fact that there is often clearing of the basilar miliary lesion with confluent breakdown and spread of the more apical infiltration.

A fascinating concept that has been propounded is that caseous, hilar lymph nodes are the etiological cause for lower lobe disease.[1,4] One idea is that there is retrograde lymphatic flow to the apex of the lower lobe; thus disease in the hilar nodes is transmitted to the apex of the lower lobe. The other more widely held idea is that caseous hilar nodes erode into the substance of the superior segment of the lower lobe or into the bronchus supplying this segment. It is well known that caseous hilar nodes do erode into the lung just as they do erode into the esophagus, blood vessels, trachea, and bronchi, and there is much pathological material demonstrating these erosions. Especially is this true in children where there are devious results such as epituberculosis, esophagotracheofistulae, esophageal diverticulae and hematogenous tuberculosis. Contributing somewhat to this concept is Auerbach's recent study,[1] in which he reviewed 1656 routine autopsies and found 26 cases with perforation of nodes into the trachea and bronchi. He states though that he does not consider this as a true incidence, for he does not know how often a progressive cavity develops at the site of an intrapulmonary perforation, the subsequent disease obliterating all signs of the rupture. One other modification of this concept is that caseous lymph nodes of the primary complex erode into the lung parenchyma during the primary stage with subsequent healing; then, later on, there can occur a breakdown of this focus in the reactivation stage.

Radiologically, the importance of "hilar" lesions must be stressed. On the x-ray EPA these lesions appear to be closely approximated to the hilar structure. Actually, these "hilar" lesions and "hilar" cavities lie far posteriorly in the superior segment. It is almost impossible to draw significant conclusions from a radiological study in most cases. There is also very little pathological support although such studies as Auerbach's do indicate that some proportion of these cases are related to eroding caseous nodes. It may be that surgical intervention may give us an earlier pathological or pathogenetic picture, but until then the concept of caseous node erosion must be questioned in most cases.

After reviewing these many concepts we must conclude that they may all play a role in the pathogenesis of lower lobe disease, and that further investigation will be helpful. We do not believe that any one mechanism will explain all the cases; rather we do believe that there are several mechanisms that can apply at different times. However, it does seem that lower lobe disease is an integral part of upper lobe disease with much similarity in pathogenesis for both.

MANAGEMENT

It is in the field of therapy that important distinction must be made between upper

and lower lobe diseases. Collapse measures, such as pneumothorax and thoracoplasty have not been found too successful in the management of this disease. The combination of large posterior "hilar cavity" with high incidence of secondary bronchiectasis and spread into other lower lobe segments would suggest poor results from these procedures. A recent study[6,7] gives poor statistical results, emphasizing the high incidence of atelectasis and pleural complications. Other recent work also points out the fact that the classical type thoracoplasty for upper lobe disease often fails because of the unsuspected presence of a superior segment cavity obscured by extensive disease of the upper lobe. Even with more attention to oblique and lateral films in upper lobe disease to bring out active disease in the superior segment it is probable that more extensive thoracoplasties will be needed to handle the paravertebral gutter cavity of the superior segment. It is, of course, not desirable to use thoracoplasty for management of pure lower lobe disease because of the unnecessary sacrificing of the entire healthy upper lobe. Similarly, with pneumothorax for localized superior segment disease, the entire lung has to be sacrificed for the small lesion, centrally located.

More recently two new approaches to therapy have been instituted, pneumoperitoneum and pulmonary resection. With pneumoperitoneum and associated streptomycin we have succeeded in halting progressive superior segment disease in most of our cases. We have used the phrenic crush as a supplemental procedure only, where subsequent follow-up suggested its need. This selective use of the phrenic crush needs stressing. Occasionally, a temporary phrenic crush together with pneumoperitoneum causes a permanent phrenic paralysis, presumably due to atrophy of muscles from overstretching. This is not too significant in pure lower lobe disease because permanent phrenic paralysis is usually utilized with resection. Where thoracoplasty will later be necessary, diaphragmatic motion is important, for without this motion there will be inhibition of drainage and predisposition toward atelectasis and other postoperative complications in the remaining basilar lung. Thus, we feel that we have a measure for controlling this type of disease. The question of long-term result is not to be answered at this time. In many sections of America the prevailing belief is that lobectomy is the procedure of choice with primary resection of the lower lobe, if disease is not too acute and if there is no other contraindication. These resection-minded individuals do, however, use pneumoperitoneum often to control acute or spreading disease, especially when the patient is too toxic for immediate surgery. Their claim for short term follow-ups are excellent. Their results, of course, will not be properly evaluated for many years. In our cases we have used pneumoperitoneum to the fullest extent. As in the management of upper lobe disease the principle of using permanent collapse measures for irreversible or severe disease is adhered to. It is often not easy to determine which disease is reversible, and so we prefer to use the more conservative procedure like pneumoperitoneum until we can be sure of the patient's response to nonsurgical management. After several months of trial with pneumoperitoneum the situation often crystallizes and persistence of a cavity or general lack of response indicates a need for resection. The principle of saving time in bed for the average patient is good and helpful, both psychologically and economically, but it must be cautioned that tuberculosis management must be aimed at that disease which is invisible by x-ray as well as that which is discernible.

The following cases are presented at this time to open for discussion newer trends in management of lower lobe tuberculosis. Despite the short follow-up,—the longest is approximately three years,—there are certain trends which we believe deserve mention. Especially is this true since the wave of resection enthusiasm which is stirring over many sections will probably reach here soon.

CASE REPORTS

Case No. 1. Twenty-six year old white male patient, admitted to the hospital on December 28, 1948, complaining of a six weeks' period of weakness, fatigability, malaise, weight loss, nonproductive cough, and afternoon fever about one degree. In addition, he also noted some mild dyspnea at rest and exertion. There was intermittent, sticking pain across his anterior chest. Patient's wife had had active tuberculosis for two and one-half years previous to this time, and during that time patient had been in close contact with her. Because of this exposure he had had x-ray films of

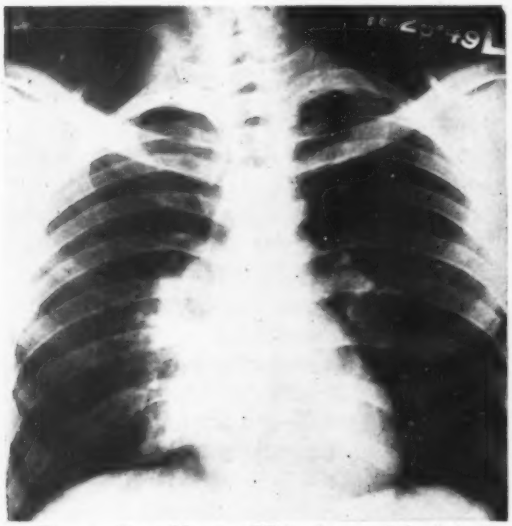

Fig. 1. Case No. 1—EPA shows "hilar" infiltration and cavitation.

Fig. 3. Right lateral view best demonstrates position of lesion.

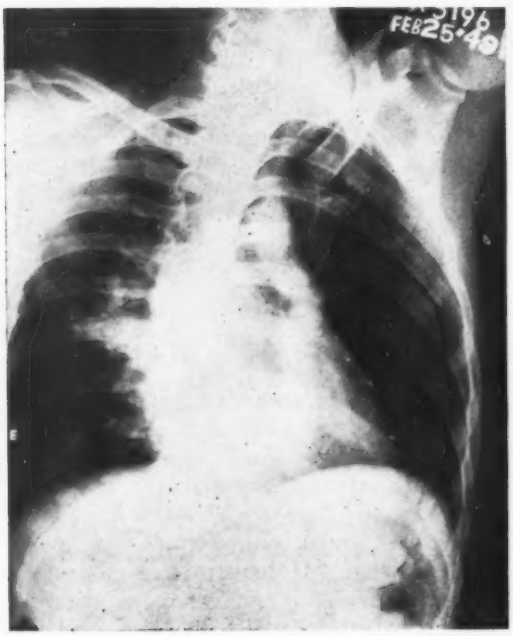

Fig. 2. Right oblique view helps place disease in the lower lobe.

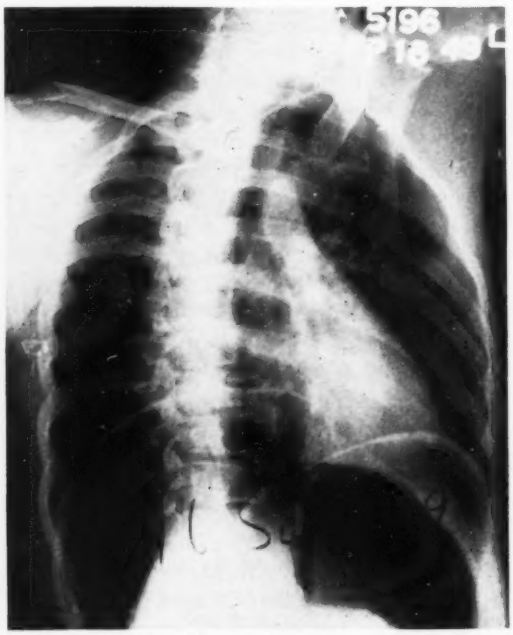

Fig. 4. Right oblique view shows improvement after pneumoperitoneum.

his chest taken every six weeks. All films were reported negative until the one taken two weeks before admission. This one revealed marked right "hilar" prominence. The patient was told to report to this hospital by an outside physician, and under close observation here during the next two months he continued to run a low grade elevation of temperature. X-ray revealed progressive enlargement of the right "hilar mass." Sputum studies for acid fast bacilli remained consistently negative until sixty days after admission. At this time there was further enlargement of the right "hilar mass" with excavation. Oblique and other projections revealed a large cavity in the middle of a caseous pneumonic process, involving the apex of the right lower lobe. At this time sputum became consistently positive for acid fast bacilli. The patient was started on streptomycin therapy, 1 gram a day for ninety days, first course starting February 23, 1949. While on the drug patient became afebrile, asymptomatic, sputum decreased in amount with marked decrease in the number of acid fast bacilli present. The cavity gradually became smaller on x-ray. In May, 1949, in an attempt to close the cavity and convert the sputum, pneumoperitoneum was instituted with good elevation of the diaphragm. Immediately thereafter the sputum became negative and has remained negative up to the present time. There was gradual resolution of the pneumonic processes in the apex of the right lower lobe. Following good elevation of the diaphragm, however, some additional infiltration could be seen extending through the right lower lobe. Though this is not extensive, it is thought that there is suggestion of activity by chest x-ray. Sputum, sedimentation rate and temperature, however, are normal.

Although good progress has been made in this case, it is too early to evaluate the results of our therapy. Suggestion of persistent lucency is stimulating the consideration of lobectomy in the near future.

Case No. 2. Twenty-four year old colored male patient, admitted to this hospital on August 17, 1948. Patient stated that he had been ill intermittently since 1945 when, in the Southwest Pacific, he developed an almost constant head and chest cold. He had lost weight gradually since that time, and at time of admission had lost a total of 40 pounds. About five months before admission, he developed a severe pleuritic pain in the right chest, and two weeks before admission he had blood-streaked sputum. He also had high fever and night sweats.

Examination on admission revealed that patient had a large tuberculous lung abcess involving apex of the right lower lobe with definite infiltration and some atelectatic process in the right lower lung field. Sputa were markedly positive for acid fast bacilli.

Patient was given 2 six-week courses of streptomycin, 1 gram daily. In addition, he received penicillin and sulfadiazine. Serial follow-up revealed diminution in the size of the lesion, and it was felt that pneumoperitoneum would be the treatment of choice to help collapse the cavity. This was begun in January 1949, and a successful pneumoperitoneum was obtained. Following these procedures the patient made very good progress. X-ray revealed closure of the cavity and marked regression of the pneumonic infiltration in the right lower lung field. Sputum converted to negative (last positive in October, 1948). Patient became asymptomatic, gained weight, and at the present time there is only small residual infiltration in the right hilar area of uncertain activity.

It has been decided that this patient shall be continued on ambulatory pneumoperitoneum as an out-patient. He has been instructed to remain on strict bed rest at home.

Case No. 3. Thirty-one year old colored male patient, admitted to the Veterans hospital on September 12, 1948, complaining of coughing up blood. Patient stated that he had been well until two weeks prior to admission when he developed a heavy chest cold, accompanied by low grade fever and a cough productive of thick white sputum. On the morning before admission patient suddenly coughed up about one pint of dark red blood mixed with sputum. X-ray on admission revealed a parahilar infiltration on the right, a diffuse pneumonic process most marked in the apex of the right lower lobe. Within this pneumonic process there were some areas of breakdown, suggestive of small lucencies. Sputum was positive repeatedly for acid fast bacilli. Patient was started on strict bed rest and given streptomycin, 1 gram daily for forty-two days, with repetition of the course for another forty-two days. Soon after starting streptomycin his sputum became negative for acid fast bacilli. In addition, there was revealed on serial film a generalized, although slow, clearing of the pulmonary process. It was felt that pneumoperitoneum would be of value and this procedure was instituted in December of 1948 with good results. Patient's sputum remained negative except for one single positive specimen obtained shortly after pneumoperitoneum was instituted. On this regime the patient showed progressive clearing of the right lung lesion. He remained completely asymptomatic clinically. It is over one year since the onset of disease and x-ray reveals very marked clearing of the pulmonary process. The patient is now being maintained at home on modified bed rest with out-patient pneumoperitoneum. His sputum remains negative and he is clinically asymptomatic.

It is felt that this disease responded well to management because there were no important areas of excavation.

Case No. 4. (Figures 5, 6, 7, 8). Twenty year old white male patient, admitted to the Veterans hospital on November 10, 1946, as a transfer from an Army General Hospital. History revealed the patient was essentially well until shortly before April, 1946, at which time he was admitted to a Regional Hospital in the Army, complaining of pain of pleuritic nature in the left side, with a productive cough of three months' duration.

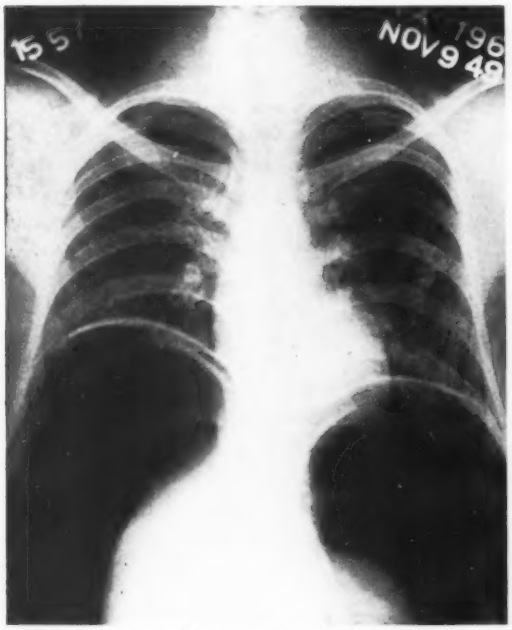

Fig. 5. Case No. 4. EPA reveals widespread basilar involvement bilaterally.

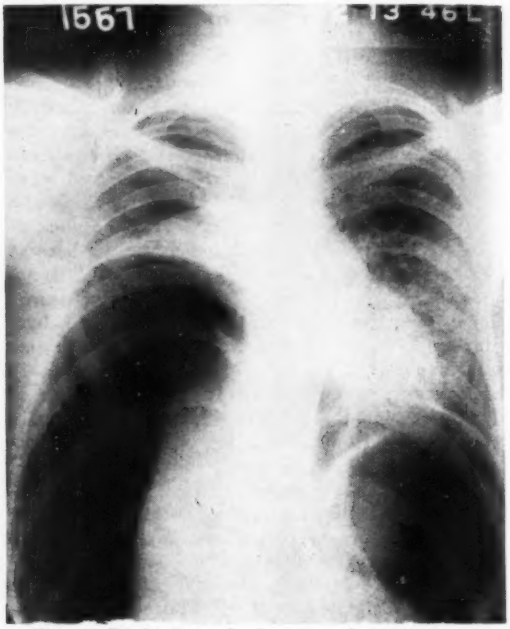

Fig. 7. Right lateral view reveals posterior position of lesions.

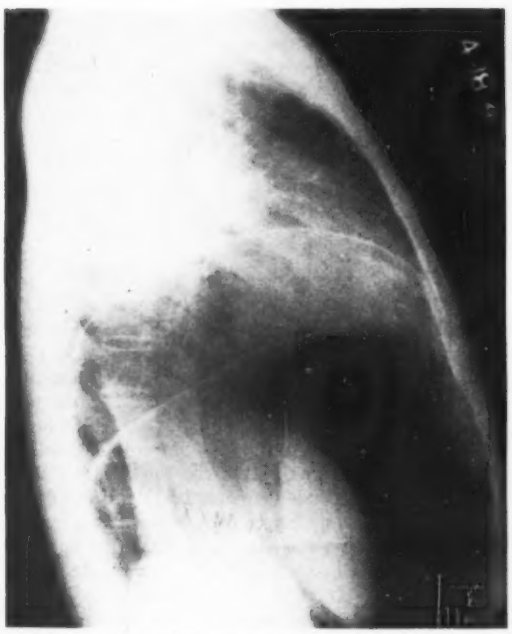

Fig. 6. EPA after pneumoperitoneum shows compression of lower lobes.

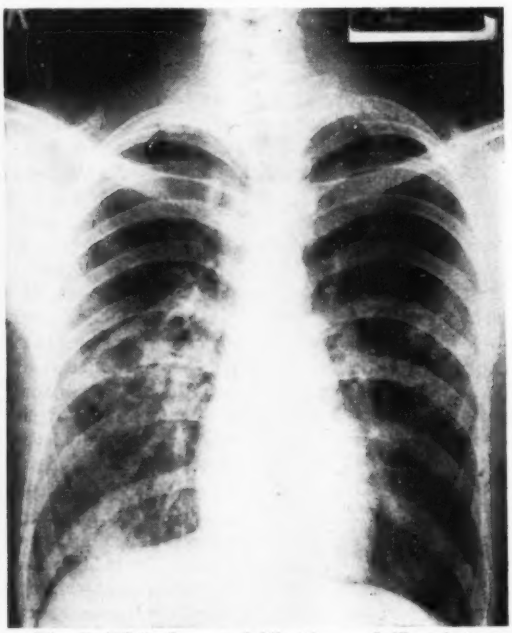

Fig. 8. EPA shows calcification and fibrosis two and a half years after onset.

Examination on admission revealed the presence of bilateral pneumonic processes with extensively excavated caseous disease in the left lower lung. The patient was started on pneumoperitoneum with right phrenic crush. Sputum was markedly positive for acid fast bacilli.

At least six months after institution of pneumoperitoneum he was transferred to this hospital. X-rays on admission here revealed marked elevation of both diaphragms, especially the right, with extensive compression of the lesions in both lower lung fields. Sputum remained positive. A course of streptomycin was started in April, 1947. This was continued for one hundred and twenty days. There was remarkable clearing in both lungs during and following the course of streptomycin. Sputum became negative in October 1947, and has remained negative until the present time. The patient gained a considerable amount of weight and remained asymptomatic. In December 1948, approximately two years after admission the patient was discharged with instructions to return as an out-patient for pneumoperitoneum. At the time of discharge there was remarkable clearing of infiltration in both lower lung fields. Only slight residual infiltration of fibrotic nature was still present in the right lower lung field. In the left lower lung field there was slightly more infiltration. At the present time, one year following discharge, the patient has continued to show good progress. Sputum is still negative and x-ray continues to show improvement.

The result from pneumoperitoneum and streptomycin in this case has been very gratifying. What would have been a hopeless case is now regarded as having a moderately good prognosis. By the time this patient was first seen and worked up, disease had involved most of the lower lobe. We feel that the disease probably started in the apex of the right lower lobe, and extensive cavitation. Then it is felt there was spill into the left lung field. We feel as if this case followed the same dynamics as did our others.

Case No. 5. Twenty-two year old colored male patient, transferred to this hospital July 2, 1949, from another institution. History revealed that the patient was in good health until January, 1948, when he developed pleurisy on the right and a cough productive of blood streaked sputum. Patient was evacuated from overseas where he had become ill and brought back to a general hospital. Examination at this hospital revealed some evidence of weight loss and a colored male, not ill appearing. Also there was revealed the presence of discrete nontender nodes in the axillae and inguinal region and also in the neck. The latter node was removed from the submandibular region and biopsy showed tuberculosis. X-ray at this time revealed extensive exudative infiltration with marked cavitation in the superior segment of the right lower lobe. In addition, there was also some infiltration in the left midlung region, thought to be in the lower portion of the left upper lobe. Patient was treated with bed rest and streptomycin and showed good response. Bronchoscopy done in July 1948, was negative for endobronchial disease, and in September pneumoperitoneum was started. In October a left phrenic crush was done. Finally, because of the presence of positive sputa, in January of 1949, and the definite cavitation in the apex of the right lower lobe he was presented to Surgical Conference for surgery of the disease in the apex of the right lower lobe. A thoracotomy was done and segmental resection of the apex of the lower lobe was done on the right. In addition, he was given a permanent phrenic paralysis. Postoperative course was uneventful. He made a fine clinical response. Sputum diminished in amount. Patient gained weight. He was given some ambulation and then transferred to this hospital for final disposition. Follow-up examinations have revealed nine negative sputum concentrates for acid fast bacilli and only one specimen showed very few acid fast bacilli. X-ray revealed stability of all lesions, no important change. It was felt, therefore, the patient could be discharged to continue bed rest and gradual ambulation at home.

Case No. 6. Twenty-seven year old white male patient, prisoner of war in Japan, admitted to this hospital September 6, 1949, after a three month illness of fever, headache, cough, hemoptysis. Local physician did sputum examinations and found them positive for acid fast bacilli. Examination at this hospital revealed the presence of exudative disease in the upper portion of the right lower lobe with numerous small lucencies present. Diagnosis of moderately advanced pulmonary tuberculosis, active, was made and the patient started on streptomycin therapy. One month later review of films revealed no important change and a pneumoperitoneum was induced. Patient is clinically asymptomatic except for productive cough from which there comes a moderate amount of sputum. He has gained 15 pounds in weight, and is otherwise clinically asymptomatic. Sputum has remained consistently positive for acid fast bacilli. It is too early to judge the results of treatment in this case.

Case No. 7. Twenty-seven year old white male patient, admitted to the hospital June 3, 1949, for an acute illness due to alcoholism. Routine chest film taken while patient was on Neuropsychiatric Service in June 1949, revealed on area of pneumonitis in the apex of the right lower lobe. The infiltration was of mixed type and showed some areas of rarefaction. Sputum examination was positive for acid fast bacilli. Careful history taken after patient was transferred off the neuropsychiatric service revealed that there had been a weight loss of 10 to 15 pounds during a period of alcoholism which lasted several months, and a cough productive of about half ounce of white sputum daily. In addition, the patient had noticed drenching night

sweats. No definite fever. One sister had been found to have arrested tuberculosis, but there had been no contact.

Physical examination was not helpful. In August a course of streptomycin was started and patient was given a right phrenic crush. During these months of observation he was generally afebrile, asymptomatic, except for a minimal cough productive of sputum positive for acid fast bacilli. On this regime there has been progressive clearing of the lesion, and sputum for the last two months has been negative by concentrate for acid fast bacilli. Patient has also been maintained on strict bed rest.

This management will be continued for the next several months and it is felt that a pneumoperitoneum will be added if the patient does not make satisfactory progress.

CONCLUSION AND SUMMARY

The cases presented are all examples of lower lobe tuberculosis—originating it is believed—in the apex of the lower lobe. Pathogenesis for this disease pattern has been discussed emphasizing the proximity of apex of lower lobe to the posterior apical and subapical portions of the upper lobe which are the most common sites of reinfection type pulmonary tuberculosis. The possible role of diaphragmatic movement has been stressed especially as the basis for preponderance of this type of disease in women. Eroding caseous nodes may play an etiological role but in a limited group. There is certainly a need for further study. Our study also confirms previous observer's findings of predominance of right sided and unilateral involvement in lower lobe tuberculosis.[8]

Management of these cases has introduced the use of pneumoperitoneum and surgical resection—lobectomy or segmental. As in all cases of pulmonary tuberculosis careful judgment is necessary, for both these procedures have their place—with timing often important. It is urged that bed rest and nonsurgical treatment not be curtailed because of the rapid rehabilitation offered by surgery. Pulmonary tuberculosis is not a localized disease. Surgery's chief indication exists in those cases that present irreversible damage and persistent focus of disease after close observation on a medical regime.

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PAROXYSMAL HYPERTENSION DUE TO NOR-EPINEPHRINE PRODUCED BY PHEOCHROMOCYTOMA

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SANFORD TUTHILL, M. D.*
THOMAS FOX, M. D.***

NEW ORLEANS

Uncomplicated paroxysmal hypertension, due to excess nor-epinephrine as a pressor substance released from a single benign medullary adrenal tumor, is a rare disease. This communication presents a classical case in which cure followed surgical extirpation of the tumor. All known diagnostic tests, with the exception of the dibenamine test of Spear and Griswold,[1] were used during the investigative studies.

REPORT OF CASE

W. S., a married woman, 40 years old, came to the Ochsner Clinic in May 1949 complaining of intermittent headaches. Six years before admission she began to have attacks of severe headache accompanied by palpitation, occurring about every two weeks. The episodes were preceded by a sensation of "blood rushing into the stomach, then to the head," and followed by a heavy pounding in

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the occipital region lasting for several minutes. Shortly after, she noticed a "hard, slow pounding of the heart," sweating, dizziness, spots before the eyes, tremors, and nervousness. Occasionally nausea, vomiting, and blurred vision occurred. Not infrequently, the patient would be awakened from sleep by a severe pain in the head. For the two years prior to admission, the attacks, which lasted from five to ten minutes, had occurred once or twice weekly. In the several weeks immediately before examination, the patient had had several attacks daily. All attacks were identical and unrelated to rest, activity, or emotional tension. The patient sought medical advice because of an attack two days previously, which lasted for fifteen minutes and was the severest attack she had experienced. It was accompanied by a strong fear of impending death.

During the initial interview the patient had a typical attack, which lasted fifteen minutes. At the onset of the attack the blood pressure was 230 mm./Hg. systolic and 120 mm./Hg. diastolic and at the end it had fallen to 144 mm./Hg. systolic and 86 mm./Hg. diastolic.

Physical examination revealed no abnormalities except mild obesity and minimal sclerosis of the retinal arterioles. Results of laboratory examinations, including hemogram, urinalysis, fecal examination, serology, basal metabolic test, and blood urea, cholesterol, and chloride determinations, as well as glucose tolerance test, were within normal limits. Roentgenograms of the chest and excretory urograms revealed no pathologic alterations. Roentgenographic examination of the skull disclosed an irregular shape of the foramen magnum. The electrocardiogram revealed no abnormality.

During preoperative hospitalization several spontaneous attacks occurred. During the first episode observed, the blood pressure was 220 mm./Hg. systolic and 150 mm./Hg. diastolic. Two days later during fist percussion of the left suprerenal area the patient had another rather typical episode. On the sixth hospital day while the examiner was talking with the patient, another spontaneous attack developed. While sitting in bed, she suddenly grimaced with pain, grabbed the back of her head, became pale, and perspired profusely. The severe headache persisted for three minutes. At the onset there was brief, irregular tachycardia followed by a slow pounding pulse. The blood pressure was 198 mm./Hg. systolic and 120 mm./Hg. diastolic. After the headache had subsided, the blood pressure fell to 126 mm./Hg. systolic and 74 mm.Hg. diastolic. The patient had many similar attacks prior to operation.

Preoperatively, according to the technic of Roth and Kvale,[2] 0.05 mg. of histamine base was injected intravenously on two separate occasions; the results are shown in figure 1. Following the same technic, a control test in which 5 cc. of psysiologic saline solution was injected intravenously resulted in normal hemodynamics (Fig. 1).

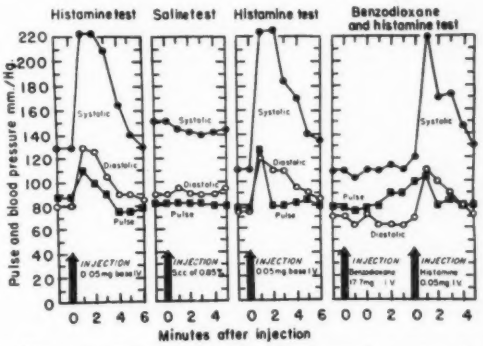

Fig. 1: Preoperative hemodynamics showing positive reaction to histamine test both with and without previously injected benzodioxane, and reaction following control test with saline.

An attempt was made to block the effect of histamine by the intravenous administration of 17.7 mg. of benzodioxane. This was followed in three minutes by 0.05 mg. of histamine base. The typical positive histamine reaction was noted (Fig. 1).

According to the procedure suggested by LaDue, Murison and Pack,[3] 400 mg. of tetra-ethyl-ammonium chloride was injected intravenously. The immediate fall in blood pressure was followed by a subsequent rise. However, this rise did not exceed the basal level. The patient did not have symptoms similar to those of the spontaneous attacks (Fig. 2).

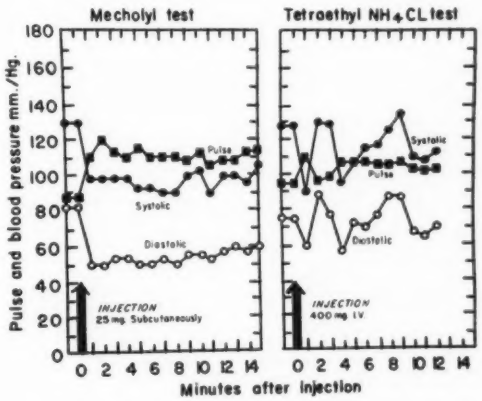

Fig. 2: Preoperative hemodynamics showing negative reactions to mecholyl and tetra-ethyl-ammonium chloride test.

Guarneri and Evans[4] stated that mecholyl chloride has shown evidence of being an epinephrine-provocative drug. The injection of 25 mg. of mecholyl chloride subcutaneously was followed by

an immediate fall in both the systolic and diastolic pressures and an increase in the pulse rate (Fig. 2). The blood pressure did not rise subsequently and a typical attack did not occur.

Epinephrine sensitivity tests were carried out with epinephrine (USP) in doses ranging from 0.05 cc. to 2 cc. Preoperative injections up to 1.5 cc. produced no remarkable symptoms and no changes in blood pressure. The injection of 2 cc., however, caused a moderate increase in blood pressure, mild headache and pounding of the heart (Fig. 3). With-

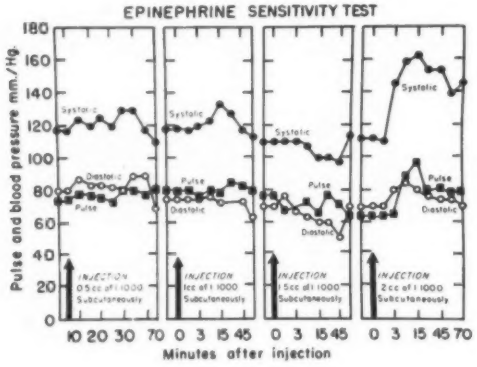

Fig. 3: Preoperative hemodynamics after injection of epinephrine (USP) in increasing dosage.

in one hour the patient was asymptomatic and the blood pressure had returned to its former level.

Exploration was performed on June 4, 1949, after induction of anesthesia with sodium pentobarbital and cyclopropane ether. The left retroperitoneal area was explored first through the usual flank incision. A soft tumor 5 by 3 by 2 cm. was discovered at the upper medial pole of the kidney. Palpation of the tumor produced a sharp rise in blood pressure (Fig. 4). The mass was excised;

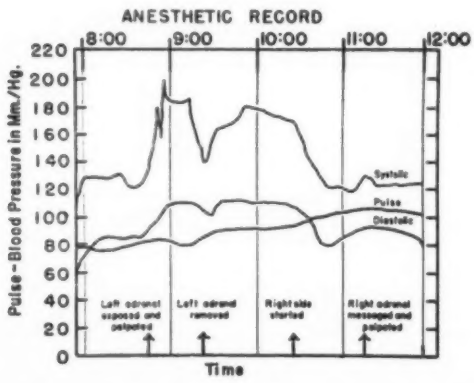

Fig. 4: Change in blood pressure and pulse during operation.

frozen section revealed it to be a pheochromocytoma. The right side was then explored. Gentle palpation of the right suprarenal gland elicited a slight rise in blood pressure.

The final microscopic examination proved the specimen to have the typical appearance of a pheochromocytoma. The tumor was immediately frozen and shipped in dry ice to Dr. Karl H. Beyer,* who reported that chemical analysis of the tumor revealed that it contained 11.8 mg./Gm. of pressor substance calculated as 1-epinephrine base. The pressor components were of the catechol ethyl amine type, such as is present in the epinephrine and nor-epinephrine structures. Additional experiments in which equipressure dosages of 1-epinephrine, 1-arterenol and the tumor extract were injected intravenously into dogs followed by the administration of dibenamine indicated that this tumor contained approximately 90 per cent of its pressor activity in the form of nor-epinephrine. The remaining 10 per cent would be considered 1-epinephrine.

Epinephrine sensitivity produced similar, but more severe, subjective symptoms following administration of 1 cc. nine days postoperatively than following injection of 2 cc. preoperatively. The objective values are shown in figure 5. The hista-

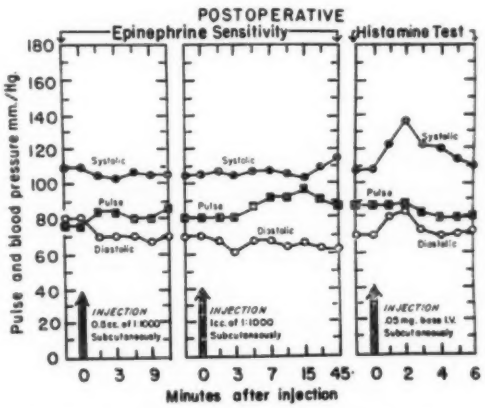

Fig. 5: Postoperative hemodynamics showing response to epinephrine test and negative reaction to histamine test.

mine test produced a considerably different result postoperatively than preoperatively (Fig. 5). The mild pressor effect is within the normal range.

The patient was discharged from the hospital on the eleventh day after an uneventful convalescence. Three months later examination revealed normal blood pressure and no recurrence of symptoms. Subsequent correspondence (nineteen months post-

*Director of Pharmacological Research, Sharp & Dohme Laboratories, Glenolden, Pa.

operatively) indicates that the patient has continued to remain well.

The hemodynamics observed in this patient during a spontaneous attack were identical with those following the intravenous injection of histamine. The immediate and abrupt rise in both the systolic and diastolic pressures, the short duration of the rise and the sudden return to normal are significant in view of recent reports on nor-epinephrine. By pharmacologic and chemical methods Holton,[5] Goldenberg and associates[6] and Calkins and coworkers[7] all found that pheochromocytomas contain from 50 to 90 per cent nor-epinephrine. Recent studies by Goldenberg and associates[8] on the hemodynamics of nor-epinephrine in human beings indicates that it acts as a general vasoconstrictor with rapid action and inactivation, whereas epinephrine acts as a general vasodilator. They also demonstrated epinephrine-norepinephrine antagonism when equal doses of each were given synchronously. They suggested that nor-epinephrine hypertension might be the result of an excess circulating nor-epinephrine due to failure of methlyation or lack of methyl donors. These observations, when applied to our patient, indicate that the pheochromocytoma released large amounts of nor-epinephrine into the blood stream periodically, and was free from the action of the antagonist, epinephrine. Likewise, this may explain the relative insensitivity to epinephrine (USP), preoperatively, when compared with the postoperative test.

The adrenolytic action of benzodioxane (933-F) has been established as a diagnostic aid in pheochromocytoma with sustained hypertension.[6] Melville[9] observed no hemodynamic change when benzodioxane (933-F) and nor-epinephrine were given simultaneously. Calkins and coworkers[7] reported almost complete inhibition of the pressor effect of an extract of a pheochromocytoma which contained large amounts of nor-epinephrine by benzodioxane (933-F) in experiments on dogs. We were unable to block the pressor response noted previously after histamine by injections of benzodioxane (933-F) three minutes prior to the intravenous administration of histamine in our patient. It has been shown that the effect of benzodioxane (933-F) lasts as long as ten minutes. The time of the injection of histamine following benzodioxane in our case appears to be well within the range of the effectiveness of the adrenolytic agent; therefore, unexplainable factors must have contributed to the failure of blocking the pressor response.

It is unfortunate that dibenamine was not used in our case, since its adrenolytic properties have been demonstrated in a case of pheochromocytoma by Spear and Griswold,[1] who, however, did not indicate the nor-epinephrine content of the tumor. The cardiovascular response to the tumor extract in our case and that of arterenol were pressor following dibenamine infusion in dogs. The tetra-ethyl-ammonium chloride test of LaDue and coworkers[3] and diagnostic aids in pheochromocytoma, all gave negative results.

Recently, Engel and von Euler[10] reported 2 cases of pheochromocytoma diagnosed preoperatively by the extraction of epinephrine and nor-epinephrine from the urine. In both cases the presence of pheochromocytoma was proved at operation, and the urinary levels of nor-epinephrine and epinephrine excretion fell to normal range postoperatively.

Metabolic disturbances have been reported in patients with pheochromocytoma and ascribed to the increased circulating epinephrine. These metabolic abnormalities have returned to normal after successful removal of the tumor. Clinically, our patient had no manifestations suggesting abnormal carbohydrate intolerance or increased metabolism, probably because of the small amount of l-epinephrine present in the tumor.

SUMMARY

A case is presented of a patient with paroxysmal hypertension produced by a pheochromocytoma which was successfully removed surgically. The tumor contained approximately 90 per cent nor-epinephrine. The histamine test for pheochromocytoma gave repeated positive results. Benzodioxane (933-F) failed to block the histamine

pressor response. Mecholyl chloride and tetra-ethyl-ammonium chloride were of no value as diagnostic aids. Results of epinephrine sensitivity tests were not conclusive. The metabolic processes in this patient were not disturbed by the nor-epinephrine paroxysmal hypertension.

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Medical and Surgical Journal

Established 1844

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SUBSCRIPTION TERMS: $4.00 per year in advance, postage paid, for the United States; $4.50 per year for all foreign countries belonging to the Postal Union.

News material for publication should be received not later than the eighteenth of the month preceding publication. Orders for reprints must be sent in duplicate when returning galley proof.

Manuscripts should be addressed to the Editor, 1430 Tulane Ave., New Orleans, La.

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DIAGNOSIS OF HISTOPLASMOSIS

In recent years the clinical and laboratory aspects of histoplasmosis have assumed increasing importance. Mention has been made in this column* of some of its epidemiological and clinical considerations. The literature on the subject is growing and much has been added which is helpful to the clinician. Difficulties in diagnosis are increased by the necessity of demonstrating the organism and by the fact that there is no characteristic syndrome.

It is clear that the disease behaves as an infectious granuloma and may produce lesions in any organ or tissue. In a recent review of 138 cases reported in the literature, Hodgson found evidence that 65 had pulmonary involvement; the remaining 73 had lesions in various organs. The diagnosis in 64 cases of the total was made at necropsy, and in 47 by biopsy. In 16, it was established by culture, and in 11, the organism was found by direct examination of suitable material, such as sputum, pleural fluid, pus, peripheral blood, and scrapings from lesions.

Cultures were reported to have a high degree of reliability, since in 71 patients, 61 had at least one positive culture. Animal inoculation was less dependable since it was positive in only 12 of 121 patients for whom it was performed.

The histoplasmin skin test was performed on 31 patients and gave positive results in only 16. It is remarked that since the test is positive on a large proportion of the normal population, and negative in half of those with the disease, it is of little diagnostic value in its present form.

The proven diagnosis was made during life in 59 of the 138 cases, or about 43 per cent. Necropsy was performed in 96 of the 138 cases; all organs were involved, and in decreasing frequency there were lesions in lymph nodes, liver, lungs, spleen, adrenal glands, intestines, bone marrow, kidneys, and oropharynx. There were 41 instances of adrenal involvement by this organism among the 96 on whom necropsy was performed. Kotcher and Leikin, reporting histoplasmosis in 7 infants under eight months old, found *Histoplasma capsulatum* in the bone marrow of 6, either on smear or culture, or both. Pratt and associates reported *H. capsulatum* in the bone marrow in 1 case.

Roentgenograms of the thorax in the review by Hodgson were reported in 48 of the 65 cases with pulmonary involvement. The description of the lesions indicated calcification, cavitation, pneumonitis, bronchitis, peribronchial infiltration, and in 4 instances, resembled the reinfection types of tuberculosis of the apices. There was nothing characteristic about the appearance roentgenographically, and it is clear that

*N. O. M. & S. J. 100:527, (May) 1948.

the lesion of pulmonary histoplasmosis may resemble almost any lesion seen in the lungs. In only 11, it was confined to one lung.

Raftery, reporting on gastrointestinal histoplasmosis in children, studied the appendices filed as surgical specimens in children (6 years of age and under) of which there were 436 appendices. Fifty-four were found to contain *H. capsulatum*. All involved appendices were the site of marked follicular hyperplasia, and the enlarged follicles showed uniform sprinkling of large phagocytic mononuclear cells which contained the organism. He reported that the Rawson modification of the Ziehl-Neelsen stain was of particular value in distinguishing nuclear debris from the *H. capsulatum*. The 51 clinical histories of the children that were available were reviewed and all but 4 showed some evidence of chronic illness.

Recovery from histoplasmosis is possible and now well authenticated. Of the 138 patients in the first review mentioned above, 23 were alive when reported on. Considering the frequency of a positive histoplasmin skin test, the number of presumably mild cases that recover must be too numerous to estimate.

As the proof of diagnosis depends upon the recognition in the laboratory of the organism in tissue or culture, special attention is needed to secure such identification. Culture of any suspected material should be made on special media. The organism may be cultured from tissues, sputum, pleural fluid, gastric contents, bronchial washings, and any material in contact with a lesion. The organism stains poorly and is mildly gram positive and is incompletely acid fast. It has been stated that only 30 per cent of the organisms retain the red stain.

The complement fixation and precipitin reactions have not proved to be very reliable because of cross reactions. They may be negative in cases of proven histoplasmosis.

Denfield and Cole reported on 502 patients in the medical wards of the Veterans Administration Hospital, Des Moines, Iowa. These patients were tested for sensitivity to histoplismin and to tuberculin, purified protein derivative. In the northern half of Iowa, 38 per cent, and in the southern half, 68 per cent, were sensitive to histoplasmin. Correspondingly, 48 and 43 per cent had positive reactions to tuberculin. They also noted that there was an increased incidence of sensitivity to histoplasmin with age, being highest in the fifth, sixth, and seventh decades.

In view of the reports mentioned, histoplasmosis should be suspected in illness of obscure cause and when there is evidence of an inflammatory process of either acute or chronic type. The substantiation of the diagnosis is afforded by biopsy or culture of material from the site of inflammation.

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

The Seventy-first Annual Meeting of the Louisiana State Medical Society will be held in New Orleans May 7-9 and our present President, Dr. George W. Wright will terminate his services as head of organized medicine in this state. This has been a most trying year with many and varied activities and problems presenting themselves for deliberation and solution. The danger of Federal Medicine with all of its faults and intrigues has ever been a threat to our freedom in the practice of medicine which we have enjoyed throughout the years. We have had to fight the powers in Washington and elsewhere to preserve that most precious freedom of private relationship which is so essential between the physician and patient.

During the past year when so many socialistic and communistic schemes, includ-

DR. GEORGE W. WRIGHT

ing the President's National Health Program, have been brought forward to force national compulsory insurance and socialized medicine upon the public as well as the medical profession, Dr. Wright has taken the leadership in the fight to combat and defeat such legislation. He has not only been active in fighting national but also state legislation as well when such legislation has been considered detrimental to organized medicine.

Dr. Wright has most ably represented the profession at many out-of-state conventions and conferences. He has also been very active in attending our district and parish society meetings and has participated in many of the private hospital staff meetings throughout the state. We have been extremely fortunate in having such an able, conscientious and willing member of our profession to assume the leadership of our Society for the past year. In fact we might well call Dr. Wright our "traveling ambassador of good will and fellowship."

Dr. Wright was born in Monroe, Louisiana, on January 16, 1892, his father, Mr. James B. Wright and his mother, Sammie Rasco, being long-time citizens of Ouachita Parish. Dr. Wright received his early education in the city schools of Monroe and Springhill, Tennessee, graduating from this latter school in 1910 prior to entering the academic department of Tulane University in 1910. He entered the Tulane School of Medicine in 1912 and graduated in 1916, receiving his degree of Doctor of Medicine. Of course, this was just the beginning of his medical education, having served since that time as a Fellow in Pathology at Mayo Clinic in 1917 and following this attending clinics in London, England, Frankfurt, Germany, Nancy, France and numerous clinics throughout this country.

During the first World War he served as Assistant to Dr. Stone, of Boston, who was Chief of Surgery at Camp Jackson, South Carolina from November 1917 to May 1918 and later was Assistant to Dr. E. W. Meredith of Pittsburgh, who was Chief of Surgery at Evacuation Hospital No. 14 AEF. During World War II Dr. Wright served as Chairman of the Fifth District Procurement Board for Physicians and Examiner for Local Board No. 2, Ouachita Parish.

Upon his return from military service in 1919 he became attending surgeon at St. Francis Sanitarium in Monroe and has been Chief of Surgery at the institution since 1929 and also Director and Chief of Surgery at the Vaughan, Wright, Bendel Clinic in Monroe. In 1940 he was appointed consultant in surgery at the Conway Memorial Hospital, Monroe, and has served in this capacity since that time. All of these positions have been filled by him with distinction and honor.

He has served in many capacities in the Ouachita Parish Medical Society and the Fifth District Medical Society, having represented both of these societies as President. He served as delegate, councilor and vice-president of the State Society prior to his election as President.

This Society should be congratulated on having had as its President a man like Dr. Wright with his ability, capacity and willingness to fight our battles.

Dr. Wright has been honored with membership in many medical organizations in

addition to his parish, district and state organizations. He is a member of the Southern Medical Association, the American Medical Association, a Fellow of the American College of Surgeons and the International College of Surgeons and a member of the Founders Group of the Surgical Association of Louisiana. His fraternity affiliations include membership in the Academic University DKE and Medical AKK. He is very active in civic and social organizations and belongs to the Rotary, Lotus and Bayou DeSiard Country Club.

Dr. Wright was married to Miss Alene Haynes, of Vicksburg, Mississippi, in 1919. He is the proud father of one son, George Wright, Jr., who is at the present time a student at the Louisiana State University Medical School.

It is felt that Dr. Wright's splendid record as President of the State Society is due to his magnetic personality, his great capability, his untiring efforts and unlimited energy and activity, and will surely be forever remembered and appreciated by the Society. The membership sincerely thank him for his splendid services and wish for him a long and happy life.

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THE REPORT OF THE PRESIDENT

During the tenure of office of your President the efforts of our State Society have been devoted to a major degree in the direction of those of the previous administration which functioned so effectively in their role among the 48 states, fighting groups in our government who were pressing for the socialization of medicine. Medicine has accepted their challenge, not as a duty, but an opportunity—a privilege if you will, to divert their wedge from further socialization and the creation of a so-called "Welfare State," a condition surely contrary to the very philosophy of the American way of life.

The outlook for American medicine and American freedom a little more than two years ago looked extremely dark. Both were under serious immediate threat and a feeling of urgency and crises was shared by almost the entire medical profession. American medicine stood practically alone in its efforts to alert the nation regarding the true nature of bills offered so efficiently and constructed so cleverly by the socializers. The nation's doctors were confronted with the challenging task of great urgency and magnitude—a task to mobilize the greatest possible support in the shortest possible time—by means of a "Grass Roots Crusade" which would give the American people the facts of this issue of compulsory versus voluntary health insurance. Perhaps American doctors became more closely united than ever before and American medicine clashed with its opponents in open contest on the field of public opinion and by taking its key directly to the people the support of thousands of non-medical organizations and millions of individuals was enlisted. The Western Legislative Conference, made up of representatives of the states west of the Mississippi River must be given due credit for the excellent work done by them in reaching into the grass roots of the nation to educate the people regarding the real issue. The great work done by this organization during the year previous to your President's administration may be greatly emphasized by the fact that the rising tide of public opinion caused by these efforts made the proponents of compulsory health insurance to, more or less, abandon their offensive during the latter months of 1950. During this time they were engaged in a variety of delaying tactics, political maneuvers, and diversionary moves—all designed to confuse the issue and to relax public vigilance and lull American doctors into a feeling of complacency. Certainly American medicine will not be fooled by such tactics.

One may recall Florida where Pepper was "Smathered," the great victory of Taft in Ohio, and victories in Illinois, North Carolina, California, etc., to get a fair idea as to what medical men and their friends, although for the most part not politicians, might exert on our citizenry. The great force exhibited here has alerted the proponents of social medicine to the possibilities of a potent organization for clean, hon-

est government where one's labors, initiative and intelligence, whether he represents the professions, labor or industry, may be properly rewarded for the good of all mankind and, in our case, to preserve the healthiest nation and the best medical system on earth.

The socializers doubtless have little faith in the ultimate passage of the old omnibus bill, the Murray-Wagner-Dingell Bill, which now has a group of names attached to it. It is being bisected, slivered, and chopped into many bills, each having a bearing on some phase of socialized medicine or related to the so-called welfare philosophy of the Washington gang. Passage of these bills in sufficient numbers would practically equal the whole bill. All of these have been or will be introduced during the present Congress and undoubtedly Mr. Truman will try again, although defeated twice, to create a cabinet post of health and education. The more recent and perhaps the most vicious of these bills introduced is that one relating to federal aid to education (S.337). This bill is being highly propagandized and much pressure is being brought on schools and colleges to force them into a sympathetic mood.

As an illustration of the attacks from the flank and of the technics used by certain federal agencies, I quote here from a recent letter published in a Dallas paper: "Letters were gotten up by the State Department and mailed to every scientist and school head in high places in the United States (probably at the taxpayers' expense). They are asked either to sign or to be sure to give it to someone who would do so . . . . This underhand method of seeking endorsement is strictly New Deal and also strictly against the law as Section 201, Title 18 of the Criminal Code would, if enforced, put every member of the Truman cabinet and many high congressmen behind the bars."

The correlation of a formidable opposition to these vicious measures has required the loyal support not only of the officers and committees of our State Society but of every member. To these officers, committees, and members, for their needed support and suggestions, their loyalty and exhibited initiative and willingness to serve in any capacity at any expense, we wish to express thanks. While complete success is not yet in sight, the skies are clearer; however, our efforts should not be lulled by the present entrenchment of the government socializers.

The American Medical Association held its annual meeting in San Francisco during June, 1950, and its interim meeting in Cleveland during December, 1950. These meetings have, of course, been reported by our delegates but one cannot fail to mention several highlights in the programs presented: Of special interest was the nationwide radio hook-up and the program of the American Medical Association for the Advancement of Medicine and Public Health. This program, a twelve-point affair, was presented to a committee from the House of Delegates for study and review. The report of this committee to the Board of Trustees of the American Medical Association, while a masterpiece both in wording and analysis should be carefully scrutinized and studied by all of us.

The highlight of the Cleveland meeting was an address to the House of Delegates and others by the President of the International Carpenters Union and Vice President of the American Federation of Labor, Mr. Hutchinson. The subject of his talk was "Socialized Medicine is No Bargain." The support of one great labor organization in our fight against socialized medicine is indeed an advance in the right direction. I would advise that each of you read this wonderful talk by Mr. Hutchinson. This latter meeting was covered thoroughly by Dr. C. Grenes Cole, Secretary-Treasurer, Dr. Max Hattaway, Chairman of the Committee on Public Relations and your President. Dr. Cole acted also as alternate to Dr. Val Fuchs, Delegate, who could not attend. Dr. J. Q. Graves, Delegate, was present at all meetings. Our Delegates have been inspiring for their suggestions, their wide knowledge of the trend of things and particularly for the high esteem in which they are held by fellow members of the House of Dele-

gates. Also at the Cleveland meeting the sum of $500,000 was set aside to help needy medical schools. This fund will be operated on the basis of a foundation to which contributions may be made. Quite a few individual donations have also been made to it.

In summing up further activities of the Society, one cannot fail to mention the very efficient and excellent work done by the numerous committees. The Congressional Committee and the Committee on Public Policy and Legislation have remained ever alert. The latter together with several members, about 25 in all, went to Baton Rouge during the meeting of the Legislature to offer a successful opposition to the perennial Chiropractic Bill. The Council on Medical Service and Public Relations has been equally active and has energetically sponsored and promoted conferences, addresses and other activities. Dr. Charles B. Odom, Chairman of the Committee on National Emergency Medical Service, has visited Washington in the interest of his committee. Dr. Ralph Talbot attended the White House Conference on Children held in Washington. The Secretary, Dr. Cole, attended a secretaries' conference in Chicago and Dr. A. V. Friedrichs, former member of the Council on Medical Service and Public Relations, has followed up the school health program which he piloted during the previous administration. Drs. Sanders, Jones and Wiginton went to Memphis in interest of the Committee on Rural Health. Numerous officers and members have addressed civic clubs, parent-teachers associations, the Association of University Women, Public Forums, etc., to further efforts to defeat federalized medicine. Dr. J. Kelly Stone has visited Washington in the interest of the Advisory Committee to Selective Service. This committee is composed of a representative from each district, Dr. Stone serving as chairman. Too much cannot be said in favor of the great work that each member of this committee has done. Their job has indeed been a thankless and time consuming one.

The Southwestern section of the Western Legislative Conference held a meeting in Fort Worth at which time voluntary health insurance was discussed. This meeting was attended by Dr. M. D. Hargrove, Dr. H. W. Boggs and myself. The various plans including Blue Cross, Blue Shield, and commercial companies were represented. A second meeting of this Southwestern group was held in Dallas at which time members of the Washington office met with the representatives from Louisiana, Arkansas, Texas and Oklahoma with the view of screening all senators and representatives from these states. The Society was represented there by President-elect, Dr. Zander and Dr. Wright.

In addition to the above your President has met with the Committee on Public Health, the Advisory Committee on Selective Service, the Committee on Scientific Work and the Committee on Journal. All visits were made and short talks as to what our State Society was doing were given before the Louisiana Academy of General Practice, the Shreveport Medical Society, the Tri-State Medical Society (Arkansas, Louisiana, Texas). The Founders Day Meeting of the Rapides Parish Medical Society and the Eighth District Society, Southwest Louisiana Graduate Medical Assembly of the Calcasieu Parish Medical Society, Fifth District Medical Society, the Mercy Hospital Staff and Southern Baptist Hospital Staff in New Orleans, Louisiana League of Nursing Education, Louisiana Practical Nurses organization meeting, New Orleans Graduate Medical Assembly and the Chamber of Commerce 25th Anniversary Dinner of the Southern Baptist Hospital in New Orleans. Two out-of-state meetings were also attended.

Removal of the offices of the Council on Medical Service and Public Relations to our executive office has increased the efficiency of all concerned, even though the work there has overwhelmingly increased during the past year.

Acting on the authority given it by unanimous vote of the Executive Committee, a committee has secured the services of Dr. C. Grenes Cole as Secretary-Treasurer of the

Society. Dr. Cole has been in office some months now and the smoothness with which things are being operated commends him very highly for this position. Dr. Talbot, who has given some thirty-three years of unselfish effort for the Society, has become Secretary-Treasurer Emeritus and will act in an advisory capacity. Dr. Talbot should feel very pleased to see the great effort which he has put out fructify and the State Society become the outstanding organization which it is today. If credit could be given to any one individual for the great expansion taken place it would certainly be due Dr. Talbot.

Many of us have thought for some time that a plan of pension should be worked out for our office help generally. Certainly some remuneration should be offered our very diligent help at the expiration of long years of service.

The Committee on Public Health, which was created during the past year, and which absorbed the function of nine other committees, being created to act as a liaison, has failed to function as such. Such component committees as the Committee on Rural Health and the Committee on Cancer, have been signally crippled. It is felt that a review of the functions of the various committees incorporated in the Committee on Public Health should be made, a more workable committee created leaving out the two committees mentioned above. Two other committees included in this committee are incorporated in our Constitution and By-Laws and therefore cannot be included in this committee without appropriate action from the House of Delegates for amendment of the Constitution and By-Laws.

In terminating this report I should like to avail myself of the opportunity to express my thanks to the Secretaries, Dr. Talbot and Dr. Cole, to the Assistant Secretary, Miss Annie Mae Shoemaker and to other assistants in the office for their invaluable advice and service given me during the past year.

RECOMMENDATIONS

1. An equitable pension plan be worked out for our office employees.

2. The Committee on Committees review the Committee on Public Health with the view of creating a more workable and efficient representation.

3. Participation in activities of the Western Legislative Conference be continued.

4. A continuance of participation in the AMA Conference of Presidents and other officers of State Societies.

George W. Wright, M. D.
President

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Third Thursday of every month	Bastrop
Natchitoches	Second Tuesday of every month	
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of every month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

POST GRADUATE PEDIATRIC COURSE IN LITTLE ROCK

A Post Graduate Pediatric Course will be given at the University of Arkansas School of Medicine, Little Rock, Arkansas, by the Pediatric Department May 14 and 15, 1951. This is a course mainly for practitioners.

Dr. Myron E. Wegman of the Louisiana State University School of Medicine, New Orleans, Louisiana, and Dr. Gilbert B. Forbes of the Southwestern Medical School, Dallas, Texas, will be the guest speakers.

All interested physicians, nurses, and public health workers are invited to attend.

No fee will be charged for this course.

TWENTY-EIGHTH ANNUAL CONVENTION OF THE WOMAN'S AUXILIARY TO THE AMA

LAST CALL for reservations for the Twenty-eighth Annual Convention of the Woman's Auxil-

iary to the American Medical Association, which will be held at Haddon Hall, Atlantic City, N. J., June 11-14.

Atlantic City extends a hearty welcome to you!

"CARE" REQUESTING MONEY FOR BOOKS FOR FOREIGN SCHOOLS

Thailand is one of 24 countries in Europe and Asia to which CARE is urging American medical men to channel new American medical books, as a means of sharing vital knowledge, through cash contributions in any amount sent to the CARE-UNESCO Book Fund, 20 Broad St., New York City, or any local CARE address. Israel, Indo-China and the Malay States have just been added to the list of countries whose medical schools and libraries can be helped through the plan. On donations of $10 or more, donors may specify the kind of book, country and specific medical institution or type of institution they want to help. CARE makes delivery in their name and returns a receipt giving the name of the recipient institution.

RESOLUTIONS OF RESPECT AND REGRET AT THE PASSING OF DR. JOSEPH EUGENE HEARD

When, on the morning of January 19, 1951, Dr. Joseph Eugene Heard breathed his last, the entire medical profession, as well as the community in general, sustained a severe shock, for Dr. Heard represented all that was finest and highest in gentlemanly qualifications, in ideal citizenship, as a loyal friend, an unexcelled surgeon and, in medical ethics, he was a model of perfection. He was devoted to his family, his lodge, his church and to his profession.

The unexpected and irreparable death of such a valuable co-worker was a distinct loss to his associates of the North Louisiana staff; he is sorely missed.

THEREFORE, BE IT RESOLVED by the staff of North Louisiana Sanitarium that we greatly deplore the passing of one so valuable and that we extend heartfelt sympathy to his bereaved widow, son, brother and other relatives; that a copy of this resolution be sent to the family, a copy spread on our minutes and one sent to New Orleans Medical and Surgical Journal..

NEW WAY USED IN KOREA TO CLEANSE G.I.'s WOUNDS

A new method for rapid cleansing of wounds under battlefield conditions is proving of "great use in the field," the commander of a medical unit at the Korean front has reported.

pHisoHex is said to cleanse more rapidly and with greater thoroughness than soap, and unlike soap, is equally effective in hard or even sea water. Suds are developed by adding repeated small amounts of water, with gentle rubbing, after the hands have been spread with the detergent.

Originally developed for operating teams in hospitals, where it has cut scrub time from ten to two minutes, pHisoHex is widely prescribed by dermatologists for patients who cannot use soap without ill effects. It is also used by nurses to prevent cross-infections in nurseries.

ANTICIPATED RULING ON PRESCRIPTION REFILLING

The following announcement has been issued by the American Pharmaceutical Association:

"We can state positively to the pharmacists of the United States that although there has been a delay in the issuance of the final ruling by the Federal Security Administration on the interpretation of the Food, Drug and Cosmetic Act with respect to filling and refilling of prescriptions, such a ruling will be handed down in due course.

"Administrator Oscar Ewing has had under consideration for several months the various comments which have been filed with him on the tentative ruling which was published in The Federal Register on December 6, 1950. A revision of the proposed ruling has been under way but it has been delayed because attorneys of the Administration who are writing the ruling have been engaged in trying important cases on the West coast.

"It is anticipated that a revised tentative ruling will be published in the near future and that further comment from the profession and industry will be asked for before the ruling is made permanent.

"The American Pharmaceutical Association is issuing this information on the highest authority at this time because unfounded rumors have been circulated to the effect that Mr. Ewing does not intend to issue a ruling because of pending legislation on the subject. It is well recognized that controversial legislation of this kind is very apt to be sidetracked until those affected can reach an agreement.

"In the meantime, it is important that the legality of the interpretation of the Food and Drug Administration of the present Food, Drug and Cosmetic Act with respect to the filling and refilling of prescriptions be determined. In a Bulletin (No. 7) issued last August, we stated: "The Association will obviously take no stand on the proposed legislation until the fundamental issue raised in the communication to the Federal Security Administrator has been settled." This is still our position.

"We believe that the issue has been clarified sufficiently to warrant the promulgation of a ruling under which the pharmacists of the United States can carry on their important prescription work without undue regulatory interference.

"If the ruling to be issued does not meet the current needs of the medical and pharmaceutical professions, further action will be taken."